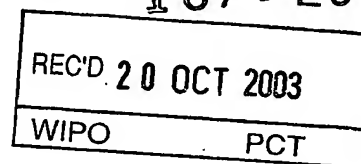


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Title: Diarylurea derivatives and their use as chloride channel blockers

IPC: -

This is to certify that the attached documents are exact copies of the above mentioned patent application as originally filed.



Patent- og Varemærkestyrelsen
Økonomi- og Erhvervsministeriet

24 September 2003

Pia Høybye-Olsen
Pia Høybye-Olsen

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PATENT- OG VAREMÆRKESTYRELSEN

**DIARYLUREA DERIVATIVES
AND THEIR USE AS CHLORIDE CHANNEL BLOCKERS**

PVS

TECHNICAL FIELD

5

The present invention relates to novel diarylurea derivatives useful as chloride channel blockers.

In other aspects the invention relates to the use of these compounds in a method for therapy, such as for the treatment of diseases responsive to modulation of the mast cell or basophil activity, diseases responsive to inhibition of angiogenesis, and sickle cell anaemia, and to pharmaceutical compositions comprising the compounds of the invention.

BACKGROUND ART

15

Chloride channels serve a wide variety of specific cellular functions and contribute to the normal function of i.a. skeletal and smooth muscle cells. Chloride channels are probably found in every cell, from bacteria to mammals. Their physiological tasks range from cell volume regulation to stabilization of the membrane potential, transepithelial or transcellular transport and acidification of intracellular organelles.

WO 97/45400, WO 98/47879, WO 00/20378 and WO 00/24707 (all NeuroSearch A/S) describe compounds, such as substituted phenyl derivatives, active as chloride channel blockers.

However, there is a strong interest in the provision of more effective and selective compounds with fewer side effects for the treatment of patients with diseases responsive to modulation of the mast cell or basophil activity, diseases responsive to inhibition of angiogenesis, and sickle cell anaemia.

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SUMMARY OF THE INVENTION

It is an object of the invention to provide novel compounds which act as chloride channel blockers.

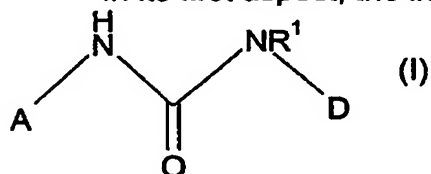
A further object of the invention is the provision of compounds with a better selectivity. A still further object is the provision of compounds with a better potency.

A further object of the invention is the provision of compounds that act on cell or tissue specific chloride channels, such as such as chloride channels of mast cells or basophils. A still further object is the provision of compounds that act on specific groups or subtypes of chloride channels.

A still further object is the provision of compound with more optimal

pharmacodynamic properties such as kinetic behaviour, bioavailability, solubility and efficacy.

In its first aspect, the invention provides a compound of general formula I,



5 or a pharmaceutically acceptable salt thereof, wherein A, R¹, and D are as defined below.

In its second aspect, the invention provides a pharmaceutical composition, comprising a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically
10 acceptable carrier, excipient or diluent.

In a further aspect, the invention provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or
15 condition is responsive to the blockade of chloride channels.

In a still further aspect, the invention relates to a method for treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to
20 responsive to blockade of chloride channels, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

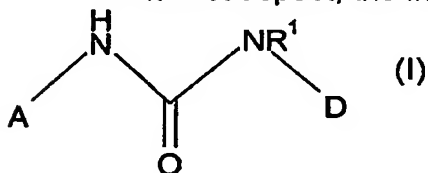
Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

25

DETAILED DISCLOSURE OF THE INVENTION

Diarylurea derivatives

In its first aspect, the invention provides a compound of general formula I,



30 or a pharmaceutically acceptable salt thereof, wherein

A represents a ring system selected from the group consisting of:

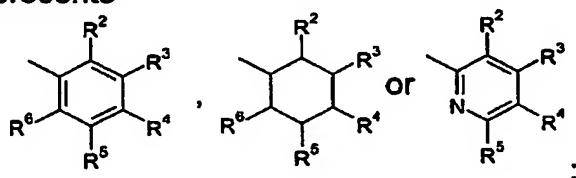
cyclohexanyl, phenyl, pyridyl, thienyl, thiazolyl, naphthyl, indolyl, pyrazolyl and oxo-pyrrolidinyl;

which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:

- 5 halogen, trifluoromethyl, nitro, alkyl, alkoxy, and phenyl; and

R^1 represents -H; and

D represents



wherein

- 10 one of R^2 , R^3 , and R^4 is selected from the group consisting of:

tetrazolyl, $-\text{COOR}^a$, $-\text{B}(\text{OH})_2$, $-\text{PO}(\text{OR}^a)_2$, $-\text{CH}_2-\text{PO}(\text{OR}^a)_2$, and $-\text{CONH}$;

wherein R^a is hydrogen or alkyl:

or R^2 and R^3 or R^3 and R^4 both represent fluoro; and

R^5 , R^6 and the remaining one or two of R^2 , R^3 and R^4 independently of each other

- 15 represent:

- hydrogen, halogen, trifluoromethyl,
- $-\text{CH}=\text{CH}-\text{COOR}^b$, $-\text{CH}_2-\text{CH}_2-\text{COOR}^b$,
- $-\text{CO}-\text{NR}^b-\text{CH}_2-\text{COOR}^c$; $-\text{CO}-\text{NR}^b\text{R}^c$,
- $-\text{CH}=\text{CH}-\text{CO}-\text{NR}^b\text{R}^c$; $-\text{CH}_2-\text{CH}_2-\text{CO}-\text{NR}^b\text{R}^c$,

- 20 ○ piperidylcarbonyl,
- $-\text{NH}-\text{CO}-\text{R}^d$ or $-\text{NH}-\text{CO}-\text{NH}-\text{R}^d$;

wherein R^d is phenyl optionally substituted with one or more substituents independently selected from halogen or trifluoromethyl; or

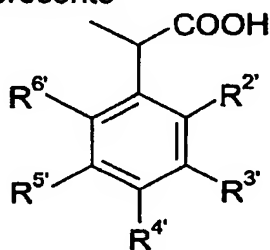
- phenyl optionally substituted with

- 25 $-\text{SO}_2-\text{NR}^b\text{R}^c$, $-\text{CO}-\text{NR}^b\text{R}^c$, $-\text{CO}-\text{NR}^b-\text{CH}_2-\text{COOR}^c$, or piperidylcarbonyl;

wherein R^b and R^c independently are hydrogen or alkyl;

or R^1 represents -H; and

D represents



wherein R^2 , R^3 , R^4 , R^5 , R^6 independently of each other represent hydrogen, halogen, or trifluoromethyl:

or R^1 together with D forms $-\text{CHR}^e-\text{CH}_2-\text{CHR}^f-\text{CH}_2-$;

wherein R^e represents $-\text{COOH}$;

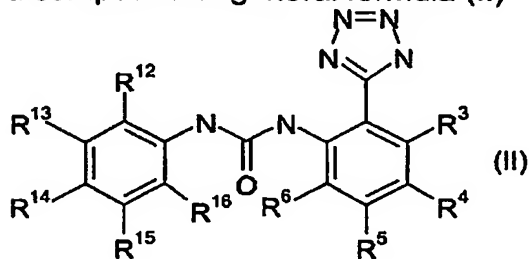
5 R^f represents hydrogen or hydroxy.

In one embodiment of the compound of general formula I, one of R^2 , R^3 and R^4 represents tetrazolyl, such as 1H-tetrazol-5-yl. In a special embodiment, R^2 represents tetrazolyl, such as 1H-tetrazol-5-yl. In a further special embodiment, R^3 represents
10 tetrazolyl, such as 1H-tetrazol-5-yl. In a further special embodiment, R^4 represents tetrazolyl, such as 1H-tetrazol-5-yl. In a further embodiment of the compound of general formula I, R^2 represents halogen, such as bromo. In a further embodiment of the compound of general formula I, R^2 and R^3 both represent halogen, such as bromo.

In a further embodiment of the compound of general formula I, A is selected
15 from the group consisting of: 1H-indol-2-yl, cyclohexyl, naphthyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, thiophen-2-yl, thiazol-2-yl, thiazol-3-yl, 2H-1 λ^4 -thiazol-2-yl, 3,6-dichloro-pyridin-4-yl, 2,6-dichloro-pyridin-4-yl, 5-chloro-pyridin-2-yl, 2-chloro-pyridin-3-yl, 5-phenyl-2H-pyrazol-3-yl, and 5-oxo-1-phenyl-pyrrolidin-3-yl.

In a further embodiment of the compound of general formula I, A is selected
20 from the group consisting of: phenyl, 2-chloro-phenyl, 2-fluoro-phenyl, 2-bromo-phenyl, 2-methoxy-phenyl, 2-trifluoromethyl-phenyl, 2,3-dichloro-phenyl, 2,4,6-trichloro-phenyl, 2,6-dichloro-phenyl, 3-bromo-phenyl, 3-chloro-phenyl, 3-iodo-phenyl, 3-methoxy-phenyl, 3-nitro-phenyl, 3,4-dichloro-phenyl, 3-fluoro-4-chloro-phenyl, 3-nitro-4-chloro-phenyl, 3-trifluoromethyl-4-chloro-phenyl, 3-trifluoromethyl-4-fluoro-phenyl, 3,5-
25 dichloro-phenyl, 3,5-difluoro-phenyl, 3-fluoro-5-trifluoromethyl-phenyl, 3,5-dimethyl-phenyl, 3,5-dimethoxy-phenyl, 3,5-bis-trifluoromethyl-phenyl, 4-chloro-phenyl, 4-methoxy-phenyl, 4-butoxy-phenyl, and 4-phenyl-phenyl.

In a further embodiment of the compound of general formula I, the compound is
30 a compound of general formula (II)



or a pharmaceutically acceptable salt thereof, wherein
 R^3 , R^4 , R^5 and R^6 independently of each other represent:

- hydrogen, halogen, trifluoromethyl,
- $-\text{CH}=\text{CH}-\text{COOR}^b$, $-\text{CH}_2-\text{CH}_2-\text{COOR}^b$,
- $-\text{CO}-\text{NR}^b-\text{CH}_2-\text{COOR}^c$; $-\text{CO}-\text{NR}^b\text{R}^c$,
- $-\text{CH}=\text{CH}-\text{CO}-\text{NR}^b\text{R}^c$; $-\text{CH}_2-\text{CH}_2-\text{CO}-\text{NR}^b\text{R}^c$,

5 ○ piperidylcarbonyl,

- $-\text{NH}-\text{CO}-\text{R}^d$ or $-\text{NH}-\text{CO}-\text{NH}-\text{R}^d$;

wherein R^d is phenyl optionally substituted with one or more substituents independently selected from halogen or trifluoromethyl; or

- phenyl optionally substituted with

10 $-\text{SO}_2-\text{NR}^b\text{R}^c$, $-\text{CO}-\text{NR}^b\text{R}^c$, $-\text{CO}-\text{NR}^b-\text{CH}_2-\text{COOR}^c$, or piperidylcarbonyl;

wherein R^b and R^c independently are hydrogen or alkyl; and

R^{12} , R^{13} , R^{14} , R^{15} , and R^6 independently of each other represent hydrogen, halogen, trifluoromethyl, nitro, alkyl, or alkoxy.

In one embodiment of the compound of general formula II, R^{12} represents
15 hydrogen. In a further embodiment, R^{12} represents halogen, such as chloro, fluoro, or bromo. In a further embodiment, R^{12} represents alkoxy, such as methoxy. In a further embodiment, R^{12} represents trifluoromethyl.

In a further embodiment of the compound of general formula II, R^{13} represents
20 halogen, such as chlorine, fluorine, bromine or iodine. In a further embodiment, R^{13} represents trifluoromethyl. In a further embodiment, R^{13} represents alkoxy, such as methoxy. In a further embodiment, R^{13} represents nitro. In a further embodiment, R^{13} represents alkyl, such as methyl. In a further embodiment, R^{13} represents hydrogen.

In a further embodiment of the compound of general formula II, R^{14} represents
25 halogen, such as chloro. In a further embodiment, R^{14} represents hydrogen. In a further embodiment, R^{14} represents alkoxy, such as methoxy or butoxy. In a further embodiment, R^{14} represents phenyl.

In a further embodiment of the compound of general formula II, R^{15} represents
30 halogen, such as fluorine or chlorine. In a further embodiment, R^{15} represents trifluoromethyl. In a further embodiment, R^{15} represents hydrogen. In a further embodiment, R^{15} represents trifluoromethyl.

In a further embodiment of the compound of general formula II, R^{16} represents
hydrogen. In a further embodiment of the compound of general formula II, R^{16} represents halogen, such as chlorine.

In a further embodiment of the compound of general formula II, R^{12} , R^{14} and R^{16}
35 each represents hydrogen. In a further embodiment of the compound of general formula II, R^{12} , R^{15} and R^{16} each represents hydrogen.

In a further embodiment of the compound of general formula II, R^5 represents
halogen, such as chlorine, and R^2 , R^3 , R^4 and R^6 each represent hydrogen.

In a still further embodiment of the compound of general formula II, R^4 and R^6 each represent halogen, such as bromine or chlorine, and R^2 , R^3 , and R^5 each represent hydrogen. In a special embodiment R^4 and R^6 each represent bromine. In a further special embodiment R^4 and R^6 each represent chlorine.

- 5 In a further embodiment of the compound of general formula II, R^4 represents $-\text{CO}-\text{NR}^b\text{R}^c$, such as $-\text{CO}-\text{NHCH}_3$, $-\text{CO}-\text{N}(\text{CH}_3)_2$ or $-\text{CO}-\text{N}(\text{CH}_2\text{CH}_3)_2$, and R^2 , R^3 , R^5 and R^6 each represent hydrogen.

- 10 In a further embodiment of the compound of general formula II, R^4 represents $-\text{CO}-\text{NR}^b-\text{CH}_2-\text{COOR}^c$, such as $-\text{CO}-\text{NH}-\text{CH}_2-\text{COOH}$, and R^2 , R^3 , R^5 and R^6 each represent hydrogen.

In a further embodiment of the compound of general formula II, R^4 represents $-\text{CH}=\text{CH}-\text{COOR}^b$, such as $-\text{CH}=\text{CH}-\text{COOH}$, and R^2 , R^3 , R^5 and R^6 each represent hydrogen.

- 15 In a further embodiment of the compound of general formula II, R^4 represents $-\text{CH}_2-\text{CH}_2-\text{COOR}^b$, such as $-\text{CH}_2-\text{CH}_2-\text{COOH}$, and R^2 , R^3 , R^5 and R^6 each represent hydrogen.

- In a further embodiment of the compound of general formula II, R^4 represents $-\text{CH}_2-\text{CH}_2-\text{CO}-\text{NR}^b\text{R}^c$, such as $-\text{CH}_2-\text{CH}_2-\text{CO}-\text{NHCH}_3$, and R^2 , R^3 , R^5 and R^6 each represent hydrogen.

In a further embodiment of the compound of general formula II, R^4 represents $-\text{CH}=\text{CH}-\text{CO}-\text{NR}^b\text{R}^c$, such as $-\text{CH}=\text{CH}-\text{CO}-\text{N}(\text{CH}_3)_2$ or $-\text{CH}=\text{CH}-\text{CO}-\text{NHCH}_3$, and R^2 , R^3 , R^5 and R^6 each represent hydrogen.

- 25 In a further embodiment of the compound of general formula II, R^4 represents piperidylcarbonyl, such as 1-piperidylcarbonyl, and R^2 , R^3 , R^5 and R^6 each represent hydrogen.

- In a further embodiment of the compound of general formula II, R^4 represents phenyl substituted with $-\text{SO}_2-\text{NR}^b\text{R}^c$, such as $-\text{SO}_2\text{N}(\text{CH}_3)_2$, and R^2 , R^3 , R^5 and R^6 each represent hydrogen. In a special embodiment, R^4 represents 4-(N,N-dimethyl-sulfamoyl)-phenyl.

- 30 In a still further embodiment of the compound of general formula II, R^4 represents phenyl substituted with $-\text{CO}-\text{NR}^b\text{R}^c$, such as $-\text{CO}-\text{N}(\text{CH}_3)_2$, $-\text{CO}-\text{NHCH}_3$ or $-\text{CO}-\text{NH}_2$, and R^2 , R^3 , R^5 and R^6 each represent hydrogen. In a special embodiment, R^4 represents 4-(N,N-dimethyl-carbamoyl)-phenyl, 4-(N-methyl-carbamoyl)-phenyl or 4-carbamoyl-phenyl.

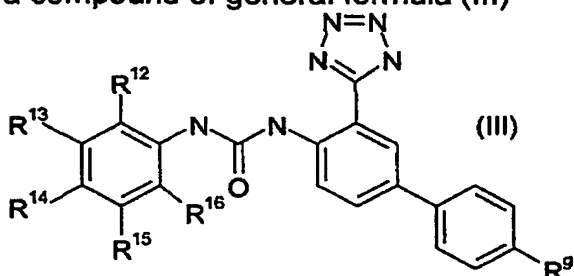
35 In a still further embodiment of the compound of general formula II, R^4 represents phenyl substituted with $-\text{CO}-\text{NR}^b-\text{CH}_2-\text{COOR}^c$, such as $-\text{CO}-\text{NH}-\text{CH}_2-\text{COOH}$ or $-\text{CO}-\text{N}(\text{CH}_3)-\text{CH}_2-\text{COOH}$, and R^2 , R^3 , R^5 and R^6 each represent hydrogen.

In a still further embodiment of the compound of general formula II, R^4 represents phenyl substituted with piperidylcarbonyl, such as 1-piperidylcarbonyl, and R^2 , R^3 , R^5 and R^6 each represent hydrogen.

In a still further embodiment of the compound of general formula II, R^4 represents
5 -NH-CO- R^d , such as -NH-CO-phenyl, and R^2 , R^3 , R^5 and R^6 each represent hydrogen.

In a still further embodiment of the compound of general formula II, R^4 represents -NH-CO-NH- R^d ; such as -NH-CO-NH-(3,5-bis-trifluoromethylphenyl), and R^2 , R^3 , R^5 and R^6 each represent hydrogen.

In a further embodiment of the compound of general formula I, the compound is
10 a compound of general formula (III)



or a pharmaceutically acceptable salt thereof, wherein

R^9 represents -CO-NR^bR^c, -CO-NR^b-CH₂-COOR^c, or piperidylcarbonyl;
wherein R^b and R^c independently are hydrogen or alkyl;

15 two of R^{12} , R^{13} , R^{14} , R^{15} , and R^{16} independently of each other represent halogen, trifluoromethyl, nitro, alkyl, or alkoxy;
and the remaining three of R^{12} , R^{13} , R^{14} , R^{15} , and R^{16} represent hydrogen.

In one embodiment of the compound of general formula III, R^{13} and R^{15}
represent trifluoromethyl and R^{12} , R^{14} and R^{16} each represents hydrogen.

20 In a second embodiment of the compound of general formula III, R^{13} and R^{15}
represent halogen, such as chlorine or fluorine, and R^{12} , R^{14} and R^{16} each represents hydrogen.

In a further embodiment of the compound of general formula III, R^{13} and R^{14}
represent halogen, such as chlorine, or trifluoromethyl, and R^{12} , R^{15} and R^{16} each
25 represents hydrogen. In a special embodiment, R^{13} represents trifluoromethyl and R^{14}
represents chlorine. In a further special embodiment, R^{13} represents chlorine and R^{14}
represents trifluoromethyl.

In a further embodiment of the compound of general formula III, R^9 represents
-CO-NR^bR^c, such as -CO-NH₂ or -CO-N(CH₃)₂.

30 In a further embodiment of the compound of general formula III, R^9 represents
-CO-NR^b-CH₂-COOR^c, such as -CO-NH₂-CH₂-COOH or -CO-NHCH₃-CH₂-COOH.

In a further embodiment of the compound of general formula III, R^9 represents
piperidylcarbonyl, such as 1-piperidylcarbonyl.

In a further embodiment of the compound of general formula I,

A represents a ring system selected from the group consisting of:

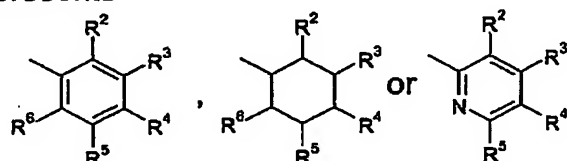
cyclohexanyl, phenyl, pyridyl, thienyl, thiazolyl, and pyrazolyl;

5 which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:

halogen, trifluoromethyl, nitro, alkyl, alkoxy, and phenyl; and

R¹ represents -H; and

D represents



wherein

R² represents -COOR^a;

wherein R^a is hydrogen or alkyl;

R³, R⁴, R⁵, and R⁶ independently of each other represent:

- 15
- hydrogen, halogen, trifluoromethyl,
 - -NH-CO-R^d or -NH-CO-NH-R^d;
- wherein R^d is phenyl optionally substituted with one or more substituents independently selected from halogen or trifluoromethyl; or
- 20
- phenyl optionally substituted with
 - SO₂-NR^bR^c, -CO-NR^bR^c, -CO-NR^b-CH₂-COOR^c, or piperidylcarbonyl;
- wherein R^b and R^c independently are hydrogen or alkyl.

In one embodiment of D, R⁵ represents halogen, such as chlorine, bromine or iodine, and R³, R⁴, and R⁶ each represent hydrogen.

25 In a second embodiment of D, R⁴ represents halogen, such as bromine or chlorine, and R³, R⁵, and R⁶ each represent hydrogen.

In a further embodiment of D, R³, R⁴, R⁵, and R⁶ each represent hydrogen.

In a further embodiment of D, R⁴ and R⁶ represent halogen, such as bromine or chlorine, and R³ and R⁵ represent hydrogen.

30 In a further embodiment of D, R² represents -COOH or -COOCH₃.

In a further embodiment of D, R⁴ represents phenyl, and R³, R⁵, and R⁶ each represent hydrogen.

In a further embodiment of D, R⁵ represents phenyl, and R³, R⁴, and R⁶ each represent hydrogen.

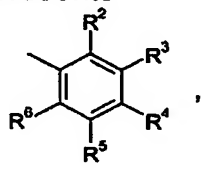
In a special embodiment, D represents 2-carboxyphenyl, 2-carboxy-4-bromophenyl, 2-carboxy-4-chlorophenyl, 2-carboxy-4-phenylphenyl, 2-carboxy-4,6-dichlorophenyl, 2-carboxy-5-chlorophenyl, 2-carboxy-5-iodophenyl, 2-carboxy-5-phenylphenyl, 2-carboxycyclohexyl, 3-carboxypyridin-2-yl, 3-carboxy-5-bromopyridin-2-yl, 2-methoxycarbonyl-5-chlorophenyl, or 2-methoxycarbonyl-4-bromophenyl.

In a further embodiment of the compound of general formula I,

A represents a phenyl optionally substituted with one or more substituents independently selected from the group consisting of

10 halogen and trifluoromethyl; and

D represents



wherein

R³ represents -COOR^a;

15 wherein R^a is hydrogen or alkyl;

R², R⁴, R⁵, and R⁶ independently of each other represent

- hydrogen, halogen, or trifluoromethyl; or
- -NH-CO-NH-R^d;

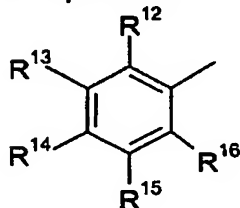
wherein R^d is phenyl optionally substituted with one or more substituents independently selected from halogen or trifluoromethyl.

20

In a special embodiment, D represents 2,5-chloro-3-carboxyphenyl, 3-carboxy-5-trifluoromethylphenyl, 3-carboxy-5-(3-bromo-phenylureido)-phenyl, or 3-carboxy-5-(3,5-dichloro-phenylureido)-phenyl.

25 In a further embodiment of the compound of general formula I,

A represents



wherein R¹², R¹³, R¹⁴, R¹⁵, and R¹⁶ independently of each other represent: halogen, trifluoromethyl, nitro, alkyl, alkoxy, or phenyl.

30

In a special embodiment R¹³ and R¹⁵ represent trifluoromethyl and R¹², R¹⁴, and R¹⁶ each represent hydrogen.

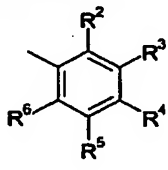
In a further embodiment of the compound of general formula I,
A represents a ring system selected from the group consisting of:
cyclohexanyl, phenyl, and pyridyl;

5 which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:

halogen, trifluoromethyl, nitro, alkyl, and alkoxy; and

R¹ represents -H; and

D represents



wherein

R² represents -B(OH)₂, -PO(OR^a)₂, -CH₂-PO(OR^a)₂, or -CONH;

wherein R^a is hydrogen or alkyl (hydrogen, methyl, ethyl);

R², R³, R⁴, R⁵, and R⁶ independently of each other represent:

15 hydrogen, halogen, trifluoromethyl, or phenyl.

In one embodiment of D, R² represents -B(OH)₂. In a second embodiment I D, R² represents -PO(OR^a)₂. In a further embodiment of D, R² represents -CH₂-PO(OR^a)₂. In a further embodiment of D, R² represents -CONH.

In a further embodiment of D, R³, R⁴, R⁵, and R⁶ each represent hydrogen.

20 In a special embodiment, D represents 2-dihydroborylphenyl, 2-phosphonophenyl, 2-phosphonomethylphenyl, 2-phosphono-4-bromophenyl, 2-phosphonomethyl-4-bromophenyl, 2-phosphonomethyl-4-chlorophenyl, 2-diethylphosphonophenyl, 2-dimethylphosphonomethylphenyl, 2-dimethylphosphonomethyl-4-chlorophenyl, or 2-diethylphosphono-4-bromophenyl.

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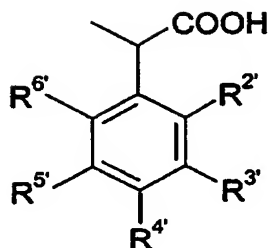
In a further embodiment of the compound of general formula I,

A represents phenyl optionally substituted with one or more substituents independently selected from the group consisting of:

halogen, trifluoromethyl, nitro, alkyl, and alkoxy;

30 R¹ represents -H; and

D represents



wherein $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, $R^{6'}$ independently of each other represent hydrogen, halogen, or trifluoromethyl.

In a special embodiment, D represents α -carboxy-4-fluorobenzyl or α -carboxy-4-trifluoromethylbenzyl.

In a further embodiment of the compound of general formula I,
A represents a ring system selected from the group consisting of:
cyclohexanyl, phenyl, and pyridyl;

10 which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:

halogen, trifluoromethyl, nitro, alkyl, and alkoxy; and
 R^1 together with D forms $-\text{CHR}^e-\text{CH}_2-\text{CHR}^f-\text{CH}_2-$;

wherein R^e represents $-\text{COOH}$;

15 R^f represents hydrogen or hydroxy.

In one embodiment, R^f represents hydrogen. In a second embodiment, R^f represents hydroxy.

In a further embodiment of the compound of general formula I,

20 A represents a ring system selected from the group consisting of:

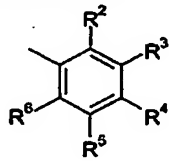
cyclohexanyl, phenyl, and pyridyl;

which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:

halogen, trifluoromethyl, nitro, alkyl, and alkoxy;

25 R^1 represents $-\text{H}$; and

D represents



wherein

R^2 and R^3 or R^3 and R^4 both represent fluoro; and

R^5 , R^6 and the remaining one or two of R^2 , R^3 and R^4 independently of each other represent hydrogen, halogen, or trifluoromethyl.

In one embodiment of D, R^2 and R^3 both represent fluoro.

In a second embodiment, R^4 , R^5 and R^6 each represent hydrogen.

- 5 In a further embodiment, R^4 represents trifluoromethyl and R^5 and R^6 represent hydrogen.

In a special embodiment, D represents 2,3-difluorophenyl or 2,3-difluoro-4-trifluoromethylphenyl.

- 10 In a still further embodiment of the compound of general formula I,

A represents a ring system selected from the group consisting of:

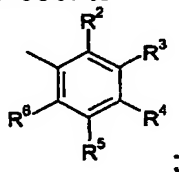
cyclohexanyl, pyridyl, and naphthyl;

which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:

- 15 halogen, trifluoromethyl, nitro, alkyl, and alkoxy;

R^1 represents -H; and

D represents



wherein

- 20 R^2 represents tetrazolyl;

R^3 , R^4 , R^5 , and R^6 independently of each other represent:

- hydrogen, halogen, trifluoromethyl; or
- phenyl substituted with
- $\text{SO}_2\text{-NR}^b\text{R}^c$, - $\text{CO-NR}^b\text{R}^c$, - $\text{CO-NR}^b\text{-CH}_2\text{-COOR}^c$, or piperidylcarbonyl;

- 25 wherein R^b and R^c independently are hydrogen or alkyl (methyl).

In a special embodiment, A is selected from cyclohexanyl, 2,6-dichloro-pyridin-4-yl, pyridin-3-yl and 3-naphthalen-1-yl; and D is selected from 3-chloro-6-(1H-tetrazol-5-yl)phenyl, 4-bromo-2-(1H-tetrazol-5-yl)phenyl, and 4'-(N,N-dimethyl-1-carbonyl)-2-(1H-tetrazol-5-yl)-biphenyl-4-yl.

30

In a special embodiment the compound of the invention is

N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[2-bromo-4-(1H-tetrazol-5-yl)-phenyl] urea;

N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[2,6-dibromo-3-(1H-tetrazol-5-yl)-phenyl] urea;

N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[2-bromo-5-(1H-tetrazol-5-yl)-phenyl] urea;

- 5-Chloro-2-[3-(1H-indol-2-yl)-ureido]-benzoic acid;
 5-Bromo-2-[3-(1H-indol-2-yl)-ureido]-benzoic acid;
 N-(3-Fluoro-5-trifluoromethyl-phenyl)-N'-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4'-sulfonic acid-dimethylamide] urea;
- 5 N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4'-sulfonic acid-dimethylamide] urea;
 N-(3,5-Difluoro-phenyl)-N'-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4'-sulfonic acid-dimethylamide] urea;
 N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
- 10 N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
 N-(3-Bromo-phenyl)-N'-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
 N-(3,5-Dichloro-phenyl)-N'-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
 N-(3-Chloro-phenyl)-N'-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
 N-(4-Fluoro-3-trifluoromethyl-phenyl)-N'-[2,4-dibromo-6-(1H-tetrazol-5-yl)-phenyl] urea;
- 15 N-(3,4-Dichloro-phenyl)-N'-[2,4-dibromo-6-(1H-tetrazol-5-yl)-phenyl] urea;
 N-(3-Methoxy-phenyl)-N'-[4'-(N'',N''-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
 N-(2-Methoxy-phenyl)-N'-[4'-(N'',N''-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
- 20 N-(4-Methoxy-phenyl)-N'-[4'-(N'',N''-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
 N-(2-Trifluoromethyl-phenyl)-N'-[4'-(N'',N''-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
 N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4'-(N'',N''-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
- 25 N-(3,5-Dichloro-phenyl)-N'-[2,4-dibromo-6-(1H-tetrazol-5-yl)-phenyl] urea;
 N-(2-Chloro-phenyl)-N'-[4'-(piperidine-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
 N-(3,5-Dichloro-phenyl)-N'-[2,4-dichloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
- 30 N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[2,4-dichloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
 N-(3,5-Difluoro-phenyl)-N'-[2,4-dichloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
 N-(3,5-Bis-trifluoromethyl)-N'-[2,4-dichloro-5-(1H-tetrazol-5-yl)-phenyl] urea;
 N-(3,5-Dichloro-phenyl)-N'-[4-(N''-methyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
- 35 N-(3,5-Difluoro-phenyl)-N'-[4-(N''-methyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
 N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4-(carbonyl-amino-acetic acid)-2-(1H-tetrazol-5-yl)-phenyl] urea;
 N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4-(acrylic acid methyl ester)-2-(1H-tetrazol-5-

- yl)-phenyl] urea;
 N-(3,5-Dichloro-phenyl)-N'-[4-(acrylic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl]
 urea;
 N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4-(acrylic acid methyl ester)-2-(1H-tetrazol-5-yl)-
 5 phenyl] urea;
 N-(3,5-Difluoro-phenyl)-N'-[4-(acrylic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl]
 urea;
 N-(2-Chloro-phenyl)-N'-[4-(acrylic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea;
 N-(4-Chloro-3-trifluoro-phenyl)-N'-[4-(propionic acid methyl ester)-2-(1H-tetrazol-5-yl)-
 10 phenyl] urea;
 N-(3,5-Dichloro-phenyl)-N'-[4-(propionic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl]
 urea;
 N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4-(propionic acid methyl ester)-2-(1H-tetrazol-5-
 yl)-phenyl] urea;
 15 N-(3,5-Difluoro-phenyl)-N'-[4-(propionic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl]
 urea;
 N-(2-Chloro-phenyl)-N'-[4-(propionic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl]
 urea;
 N-(3,5-Dichloro-phenyl)-N'-[4-(N''-malonamic acid)-2-(1H-tetrazol-5-yl)-phenyl] urea;
 20 N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4-(N-malonamic acid)-2-(1H-tetrazol-5-yl)-
 phenyl] urea;
 N-(3,5-Difluoro-phenyl)-N'-[4-(N''-malonamic acid)-2-(1H-tetrazol-5-yl)-phenyl] urea;
 N-(2-Chloro-phenyl)-N'-[4-(N''-malonamic acid)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p.
 158-160°C;
 25 N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4-[(N'',N''-dimethyl)-acrylamide]-2-(1H-tetrazol-
 5-yl)-phenyl] urea;
 N-(3,5-Difluoro-phenyl)-N'-[4-[(N'',N''-dimethyl)-acrylamide]-2-(1H-tetrazol-5-yl)-
 phenyl] urea;
 N-(2-Chloro-phenyl)-N'-[4-[(N'',N''-dimethyl)-acrylamide]-2-(1H-tetrazol-5-yl)-phenyl]
 30 urea;
 N-(3,5-Dichloro-phenyl)-N'-[4-[(N''-methyl)-acrylamide]-2-(1H-tetrazol-5-yl)-phenyl]
 urea;
 N-(3,5-Difluoro-phenyl)-N'-[4-[(N''-methyl)-acrylamide]-2-(1H-tetrazol-5-yl)-phenyl]
 urea;
 35 N-(2-Chloro-phenyl)-N'-[4-(piperidine-1-carbonyl)-2-(1H-tetrazol-5-yl)-phenyl] urea;
 N-(3,5-Dichloro-phenyl)-N'-[4-(N'',N''-diethyl-carboxamide)-2-(1H-tetrazol-5-yl)-
 phenyl] urea;
 N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4-(N'',N''-diethyl-carboxamide)-2-(1H-tetrazol-5-
 yl)-phenyl] urea;

- N-(3,5-Difluoro-phenyl)-N'-[4-(N'',N''-diethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
- N-(2-Chloro-phenyl)-N'-[4-(N'',N''-diethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
- 5 N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4-(piperidine-1-carbonyl)-2-(1H-tetrazol-5-yl)-phenyl] urea;
- N-(3,5-dichloro-phenyl)-N'-[4-(piperidine-1-carbonyl)-2-(1H-tetrazol-5-yl)-phenyl] urea;
- N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4-(piperidine-1-carbonyl)-2-(1H-tetrazol-5-yl)-phenyl] urea;
- 10 N-(3,5-Difluoro-phenyl)-N'-[4-(piperidine-1-carbonyl)-2-(1H-tetrazol-5-yl)-phenyl] urea;
- N-(3,5-Dichloro-phenyl)-N'-[4'-(carbonyl-(N''-methyl)amino-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
- N-(3,5-Dichloro-phenyl)-N'-[4-(N'',N''-dimethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
- 15 N-(3,5-Difluoro-phenyl)-N'-[4-(N'',N''-dimethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
- N-(4-Chloro-3-trifluoromethyl)-N'-[4-(N'',N''-diethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
- N-(2-Chloro-phenyl)-N'-[4'-(carbonyl-amino-acetic acid)-2-(1H-tetrazol-5-yl)-4-
- 20 biphenyl] urea;
- N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4-(N''-methyl-propylamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
- N-(3,5-Dichloro-phenyl)-N'-[4-(N''-methyl-propylamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
- 25 N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4-(N''-methyl-propylamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
- N-(3,5-Difluoro-phenyl)-N'-[4-(N''-methyl-propylamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
- N-(2-chloro-phenyl)-N'-[4-(N''-methyl-propylamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
- 30 N-(2,6-Dichloro-phenyl)-N'-[2,4-dichloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
- N-(2,4,6-trichloro-phenyl)-N'-[2,4-dichloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
- N-(3,5-Dichloro-phenyl)-N'-[4-benzamide-2-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
- N-(3,5-Difluoro-phenyl)-N'-[4-benzamide-2-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
- N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4-benzamide-2-chloro-6-(1H-tetrazol-5-yl)-
- 35 phenyl] urea;
- N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4-benzamide-2-(1H-tetrazol-5-yl)-phenyl] urea;
- N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4-(N'',N''-dimethyl acryl-amide)-2-(1H-tetrazol-5-yl)-phenyl] urea;

- N-(3,5-dichloro-phenyl)-N'-[4-(N'',N''-dimethyl acryl-amide)-2-(1H-tetrazol-5-yl)phenyl] urea;
- N-(3-Chloro-4-fluoro-phenyl)-N'-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4'-sulfonic acid-dimethylamide] urea;
- 5 N-(4-Fluoro-3-trifluoromethyl-phenyl)-N'-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4'-sulfonic acid-dimethylamide] urea;
- N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4'-carboxylic acid dimethylamide] urea;
- N-(3,5-Dichloro-phenyl)-N'-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4'-carboxylic acid
- 10 dimethylamide] urea;
- N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4'-(piperidine-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
- N-(3,5-Dichloro-phenyl)-N'-[4'-(piperidine-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
- 15 N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4'-(piperidine-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
- N-(3,5-Difluoro-phenyl)-N'-[4'-(piperidine-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
- N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4'-carboxamide-2-(1H-tetrazol-5-yl)-4-
- 20 biphenyl] urea;
- N-(3,5-Dichloro-phenyl)-N'-[4'-carboxamide-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
- N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4'-carboxamide-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
- N-(3,5-Difluoro-phenyl)-N'-[4'-carboxamide-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
- 25 N-(3,5-Dichloro-phenyl)-N'-[4'-(carbonyl-amino-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
- N-(3,5-Difluoro-phenyl)-N'-[4'-(carbonyl-amino-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
- N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4'-[carbonyl-(N''-methyl)-amino-acetic acid]-
- 30 2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
- N-(3,5-Dichloro-phenyl)-N'-[4'-[carbonyl-(N''-methyl)-amino-acetic acid]-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
- N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4'-[carbonyl-(N''-methyl)-amino-acetic acid]-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
- 35 N-(3,5-Difluoro-phenyl)-N'-[4'-(carbonyl-amino-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
- N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4'-(N''-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
- N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4'-(N''-acetic acid)-2-(1H-tetrazol-5-yl)-4-

- biphenyl] urea;
 4-Chloro-2-(3-cyclohexyl-ureido)-benzoic acid;
 5-Bromo-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]-benzoic acid;
 2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-cyclohexanecarboxylic acid;
 5 5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzoic acid;
 5-Bromo-2-[3-(3-bromo-phenyl)-ureido]-benzoic acid;
 5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]-benzoic acid;
 5-Bromo-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]-benzoic acid;
 N-(3,5-Bis-trifluoromethyl-phenyl)-N'-(phenyl-2-boronic acid) urea;
 10 N-(4-Chloro-3-fluoro-phenyl)-N'-(phenyl-2-boronic acid) urea;
 N-(3,5-Dichloro-phenyl)-N'-(phenyl-2-boronic acid) urea;
 N-Cyclohexyl-N'-(phenyl-2-boronic acid) urea;
 5-Chloro-2-[3-(pyridin-3-yl)-ureido]-benzoic acid;
 5-Bromo-2-[3-(pyridin-3-yl)-ureido]-benzoic acid;
 15 3,5-Dichloro-2-[3-(3,5-dichloro-phenyl)-ureido]-benzoic acid;
 3,5-Dichloro-2-[3-(3-chloro-4-fluoro-phenyl)-ureido]-benzoic acid;
 3,5-Dichloro-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]-benzoic acid;
 3,5-Dichloro-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzoic acid;
 3,5-Dichloro-2-[3-(4-fluoro-3-trifluoromethyl-phenyl)-ureido]-benzoic acid;
 20 3,5-Dichloro-2-[3-(3-fluoro-5-trifluoromethyl-phenyl)-ureido]-benzoic acid;
 3,5-Dichloro-2-[3-(3,5-difluoro-phenyl)-ureido]-benzoic acid;
 2-[3-(Thiophen-2-yl)-ureido]-benzoic acid;
 2-[3-(Pyridin-4-yl)-ureido]-benzoic acid;
 4-Chloro-2-[3-(pyridin-4-yl)-ureido]-benzoic acid;
 25 5-Bromo-2-[3-(pyridin-4-yl)-ureido]-benzoic acid;
 2-[3-(Pyridin-3-yl)-ureido]-nicotinic acid;
 2-[(3-(3-Chloro-phenyl)-ureido)-cyclohexanecarboxylic acid;
 2-[(3-(3-Bromo-phenyl)-ureido)-cyclohexanecarboxylic acid;
 2-[3-(3,5-Dichloro-phenyl)-ureido]-cyclohexanecarboxylic acid;
 30 2-(3-Cyclohexyl-ureido)-cyclohexanecarboxylic acid;
 2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-cyclohexane carboxylic acid;
 4-Chloro-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]-benzoic acid;
 5-Bromo-2-[3-(3-chloro-phenyl)-ureido]-benzoic acid;
 2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-nicotinic acid;
 35 5-Bromo-2-(3-cyclohexyl-ureido)-benzoic acid;
 2-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]-cyclohexanecarboxylic acid;
 2-[3-(3-Chloro-phenyl)-ureido]-cyclohexanecarboxylic acid;
 2-[3-(3-Bromo-phenyl)-ureido]-cyclohexanecarboxylic acid;
 2-[3-(2,6-Dichloro-phenyl)-ureido]-cyclohexanecarboxylic acid;

- 2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-cyclohexanecarboxylic acid;
4-Chloro-2-[3-(thiazol-2-yl)-ureido]-benzoic acid methyl ester;
5-Bromo-2-[3-(pyridin-2-yl)-ureido]-benzoic acid methyl ester;
4-Chloro-2-[3-(5-chloro-pyridin-2-yl)-ureido]benzoic acid;
5 5-Bromo-2-(3-thiazol-2-yl-ureido)-benzoic acid methyl ester;
2-[3-(5-Bromo-pyridin-3-yl)-ureido]-4-chloro-benzoic acid;
5-Bromo-2-[3-(pyridin-2-yl)-ureido]-benzoic acid;
3-Bromo-2-[3-(2H-1 λ ⁴-thiazol-2-yl)-ureido]-benzoic acid;
3-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]-biphenyl-4-carboxylic acid amide;
10 4-[3-(3,5-Dichloro-phenyl)-ureido]-biphenyl-3-carboxylic acid;
4-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-biphenyl-3-carboxylic acid;
4-[3-(3,5-Difluoro-phenyl)-ureido]-biphenyl-3-carboxylic acid;
4-[3-(2-Chloro-phenyl)-ureido]-biphenyl-3-carboxylic acid;
4-Chloro-2-[3-(5-phenyl-2H-pyrazol-3-yl)-ureido]-benzoic acid;
15 2-[3-(2-chloro-pyridin-3-yl)-ureido]-nicotinic acid;
4-Chloro-2-[3-(2-chloro-pyridin-3-yl)-ureido]-benzoic acid;
2-[3-(4-Chloro-phenyl)-ureido]-5-iodo-benzoic acid;
5-Chloro-2-[3-(5-oxo-1-phenyl-pyrrolidin-3-yl)-ureido]-benzoic acid;
5-Bromo-2-(3-phenyl-ureido)-benzoic acid;
20 5-Bromo-2-[3-(2-fluoro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(2-chloro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3,5-dimethyl-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3,5-difluoro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3,5-dimethoxy-phenyl)-ureido]-benzoic acid;
25 5-Bromo-2-[3-(2,6-dichloro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(2-bromo-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(4-chloro-3-nitro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(4-butoxide-phenyl)-ureido]-benzoic acid;
5-Chloro-2-[3-(2-chloro-phenyl)-ureido]-benzoic acid;
30 5-Chloro-2-[3-(3,5-dimethyl-phenyl)-ureido]-benzoic acid;
2-[3-(4-Biphenyl)-ureido]-5-bromo-benzoic acid;
5-Chloro-2-[3-(3-iodo-phenyl)-ureido]-benzoic acid;
5-Chloro-2-(3-phenyl-ureido)-benzoic acid;
5-Chloro-2-[3-(2-fluoro-phenyl)-ureido]-benzoic acid;
35 5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-nicotinic acid;
5-Bromo-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]-nicotinic acid;
5-Chloro-2-[3-(3,5-difluoro-phenyl)-ureido]-benzoic acid;
5-Chloro-2-[3-(3,5-dimethoxy-phenyl)-ureido]-benzoic acid;
5-Chloro-2-[3,4-dichloro-phenyl)-ureido]-benzoic acid;

- 2-[3-(4-Butoxy-phenyl)-ureido]-5-chloro- benzoic acid;
 5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]-nicotinic acid;
 3,5-Bis-[3-(3,5-difluoro-phenyl)-ureido]- benzoic acid;
 5-Bromo-2-[3-(3,5-difluoro-phenyl)-ureido]-nicotinic acid;
 5 5-Bromo-2-[3-(2,4,6-trichloro-phenyl)-ureido]-nicotinic acid;
 5-Chloro-2-[3-(2,6-dichloro-phenyl)-ureido]-benzoic acid;
 2,5-Dichloro-3-[3-(3-bromo-phenyl)-ureido]-benzoic acid;
 2,5-Dichloro-3-[3-(3,5-dichloro-phenyl)-ureido]-benzoic acid;
 3,5-Bis-[3-(3-bromo-phenyl)-ureido]- benzoic acid
 10 3,5-Bis-[3-(3,5-dichloro-phenyl)-ureido]- benzoic acid;
 3-[3-(3-Bromo-phenyl)-ureido]-5-trifluoro-benzoic acid;
 3-[3-(3,5-Dichloro-phenyl)-ureido]-5-trifluoro-benzoic acid;
 3,5-Bis-[3-(3,5-bis-trifluoromethylphenyl)-ureido]- benzoic acid;
 2-[3-(Pyridin-3-yl)-ureido]-phenyl-boronic acid;
 15 2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-phenyl-boronic acid;
 2-[3-(3-Bromo-phenyl)-ureido]-phenyl-dihydroxy-borane;
 {2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
 {2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid;
 {2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
 20 {2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid
 {2-[3-(3-chloro-phenyl)-ureido]-phenyl}-phosphonic acid diethyl ester;
 {2-[3-(3-chloro-phenyl)-ureido]phenyl}-phosphonic acid;
 {2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
 {2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid;
 25 {2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
 {2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid;
 {5-Bromo-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl
 ester;
 {5-Bromo-2-[3-(3,5 bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid;
 30 {5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid
 diethyl ester;
 {5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid;
 {5-Bromo-2-[3-(3-chloro-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
 {5-Bromo-2-[3-(3-chloro-phenyl)-ureido]phenyl}-phosphonic acid;
 35 {5-Bromo-2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
 {5-Bromo-2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid;
 {5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
 {5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid;

- {5-Bromo-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]phenyl}-phosphonic acid diethyl ester;
 {5-Bromo-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]phenyl}-phosphonic acid;
 2-[[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl]-phosphonic acid dimethyl ester;
- 5 2-[[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl]-phosphonic acid;
 2-[[3-(3,5-dichloro-phenyl)-ureido]-benzyl]-phosphonic acid dimethyl ester;
 2-[[3-(3,5-Dichloro-phenyl)-ureido]-benzyl]-phosphonic acid;
 2-[[3-(3-Phenyl-ureido)-benzyl]-phosphonic acid dimethyl ester;
 2-[[3-(3-Phenyl-ureido)-benzyl]-phosphonic acid;
- 10 2-[3-(4-Chloro-phenyl)-ureido]-benzyl]-phosphonic acid dimethyl ester;
 2-[3-(4-Chloro-phenyl)-ureido]-benzyl]-phosphonic acid;
 2-[[3-(3,4-Dichloro-phenyl)-ureido]-benzyl]-phosphonic acid dimethyl ester;
 2-[[3-(3,4-Dichloro-phenyl)-ureido]-benzyl]-phosphonic acid;
 {5-Chloro-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl]-phosphonic acid
- 15 dimethyl ester;
 {5-Chloro-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl]-phosphonic acid;
 {5-Chloro-2-[3-(3,5-dichloro-phenyl)-ureido]-benzyl]-phosphonic acid dimethyl ester;
 {5-Chloro-2-[3-(3,5-dichloro-phenyl)-ureido]-benzyl]-phosphonic acid;
 {5-Chloro-2-(3-phenyl-ureido)-benzyl]-phosphonic acid dimethyl ester;
- 20 {5-Chloro-2-(3-phenyl-ureido)-benzyl]-phosphonic acid;
 {5-Chloro-2-[3-(3,4-dichloro-phenyl)-ureido]-benzyl]-phosphonic acid dimethyl ester;
 {5-Chloro-2-[3-(4-chloro-phenyl)-ureido]-benzyl]-phosphonic acid;
 {5-Chloro-2-[3-(3,4-dichloro-phenyl)-ureido]-benzyl]-phosphonic acid dimethyl ester;
 {5-Chloro-2-[3-(3,4-dichloro-phenyl)-ureido]-benzyl]-phosphonic acid;
- 25 {2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-phenyl}-phosphonic acid diethyl ester;
 {2-[3-(2-Trifluoromethyl-phenyl)-ureido]-phenyl}-phosphonic acid diethyl ester;
 {2-[3-(2-Trifluoromethyl-phenyl)-ureido]-phenyl}-phosphonic acid;
 3-[3-(3,5-Dichloro-phenyl)-ureido]-biphenyl-4-carboxylic acid amide;
 3-[3-(2,3-Dichloro-phenyl)-ureido]-biphenyl-4-carboxylic acid amide;
- 30 3-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-biphenyl-4-carboxylic acid amide;
 {2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-phenyl}-phosphonic acid;
 [3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid;
 [3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-(5-trifluoromethyl-phenyl)-acetic acid;
 [3-(4-Chloro-3-fluoro-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid;
- 35 [3-(3,5-Dichloro-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid;
 [3-(3-Chloro-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid;
 1-(3,5-Bis-trifluoromethyl-phenylcarbamoyl)-pyrroline-2-carboxylic acid;
 1-(3,5-Bis-trifluoromethyl-phenylcarbamoyl)-4-hydroxy-pyrroline-2-carboxylic acid;
 1-(4-Chloro-3-trifluoromethyl-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid;

- 1-(3-Chloro-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid;
 1-(3-Bromo-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid;
 1-(3,5-Dichloro-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid;
 1-(Cyclohexyl-carbamoyl)-pyrrolidine-2-carboxylic acid;
 5 1-(2,6-Dichloro-pyridin-4-ylcarbamoyl)-pyrrolidine-2-carboxylic acid;
 1-(4-Chloro-3-trifluoromethyl-phenylcarbamoyl)-4-hydroxy-pyrrolidine-2-carboxylic acid;
 1-(3-Chloro-phenylcarbamoyl)-4-hydroxy-pyrrolidine-2-carboxylic acid;
 1-(3-Bromo-phenylcarbamoyl)-4-hydroxy-pyrrolidine-2-carboxylic acid;
 1-(Pyridin-3-ylcarbamoyl)-pyrrolidine-2-carboxylic acid;
 10 N-Cyclohexyl-N'-(2,3-difluoro-4-trifluoromethyl-phenyl) urea;
 N-Cyclohexyl-N'-(2,3-difluoro-phenyl) urea;
 N-(2,3-Difluoro-4-trifluoromethyl-phenyl)-N'-(pyridin-3-yl) urea;
 N-(Pyridin-3-yl)-N'-(2,3-difluoro-phenyl) urea;
 N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-(2,3-difluoro-4-trifluoromethyl-phenyl) urea;
 15 N-(2,6-Dichloro-pyridin-4-yl)-N'-(2,3-difluoro-4-trifluoromethyl-phenyl) urea;
 N-(2,3-Difluoro-4-trifluoromethyl-phenyl)-N'-(pyridin-4-yl) urea;
 N-(2,3-Difluoro-phenyl)-N'-(pyridin-4-yl) urea;
 N-(Cyclohexyl)-N'-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
 N-(2,6-Dichloro-pyridin-4-yl)-N'-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
 20 N-Cyclohexyl-N'-[4'-(N'',N''-dimethyl-1-carbonyl)-2-(1H-tetrazol-5-yl)-biphenyl-4-yl]
 urea;
 N-(2,6-Dichloro-pyridin-4-yl)-N'-[4'-(N'',N''-dimethyl-1-carbonyl)-2-(1H-tetrazol-5-yl)-
 biphenyl-4-yl] urea;
 N-Cyclohexyl-N'-[4-bromo-2-(1H-tetrazol-5-yl)-phenyl] urea;
 25 N-(2,6-Dichloro-pyridin-4-yl)-N'-[4-bromo-2-(1H-tetrazol-5-yl)-phenyl] urea;
 N-[5-Chloro-2-(1H-tetrazol-5-yl)-phenyl]-N'-(pyridin-3-yl) urea;
 N-[4-Bromo-2-(1H-tetrazol-5-yl)-phenyl]-N'-(pyridin-3-yl) urea;
 N-(Naphthalen-1-yl)-N'-[4'-(N'',N''-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-
 4-yl] urea;
 30 N-[2,4-Dibromo-6-(1H-tetrazol-5-yl)-phenyl]-N'-(2,6-dichloro-pyridin-4-yl) urea;
 or a pharmaceutically acceptable salt thereof.

Definition of Substituents

In the context of this invention halogen represents a fluorine, a chlorine, a
 35 bromine or an iodine atom.

Alkyl means a straight chain or branched chain of one to six carbon atoms, including but not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, and hexyl; methyl, ethyl, propyl and isopropyl are preferred groups.

Alkoxy is O-alkyl, wherein alkyl is as defined above.

Amino is NH_2 or NH-alkyl or N-(alkyl)_2 , wherein alkyl is as defined above.

Steric Isomers

The chemical compounds of the present invention may exist in (+) and (-) forms as well as in racemic forms. The racemates of these isomers and the individual isomers themselves are within the scope of the present invention.

Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the diastereomeric salts is by use of an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optical active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example.

The chemical compounds of the present invention may also be resolved by the formation of diastereomeric amides by reaction of the chemical compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric carbamates by reaction of the chemical compound of the present invention with an optically active chloroformate or the like.

Additional methods for the resolving the optical isomers are known in the art. Such methods include those described by *Jaques J, Collet A, & Wilen S* in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optical active compounds can also be prepared from optical active starting materials.

Pharmaceutically Acceptable Salts

The chemical compound of the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically (i.e. physiologically) acceptable salts, and pre- or prodrug forms of the chemical compound of the invention.

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydrochloride, the hydrobromide, the nitrate, the perchlorate, the phosphate, the sulphate, the formate, the acetate, the aconate, the ascorbate, the benzenesulphonate, the benzoate, the cinnamate, the citrate, the embonate, the enantate, the fumarate, the glutamate, the glycolate, the lactate, the maleate, the malonate, the mandelate, the methanesulphonate, the naphthalene-2-sulphonate derived, the phthalate, the salicylate, the sorbate, the stearate, the succinate, the

tartrate, the toluene-p-sulphonate, and the like. Such salts may be formed by procedures well known and described in the art.

Metal salts of a chemical compound of the invention include alkali metal salts such as the sodium salt of a chemical compound of the invention containing a carboxy
5 group.

Methods of Preparation

The compounds of the invention may be prepared by conventional methods for chemical synthesis, e.g. those described in the working examples. The starting
10 materials for the processes described in the present application are known or may readily be prepared by conventional methods from commercially available chemicals.

Also one compound of the invention can be converted to another compound of the invention using conventional methods.

The end products of the reactions described herein may be isolated by
15 conventional techniques, e.g. by extraction, crystallisation, distillation, chromatography, etc.

Pharmaceutical Compositions

In another aspect the invention provides novel pharmaceutical compositions
20 comprising a therapeutically effective amount of a compound of the invention.

While a compound of the invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers,
25 buffers, diluents, and/or other customary pharmaceutical auxiliaries.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising a compound of the invention, or a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers therefore, and, optionally, other therapeutic and/or prophylactic ingredients, know and
30 used in the art. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

The pharmaceutical composition of the invention may be administered by any convenient route, which suit the desired therapy. Preferred routes of administration include oral administration, in particular in tablet, in capsule, in dragé, in powder, or in
35 liquid form, and parenteral administration, in particular cutaneous, subcutaneous, intramuscular, or intravenous injection. The pharmaceutical composition of the invention can be manufactured by any skilled person by use of standard methods and conventional techniques appropriate to the desired formulation. When desired, compositions adapted to give sustained release of the active ingredient may be

employed.

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

5 The actual dosage depend on the nature and severity of the disease being treated, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.1 to about 500 mg of active ingredient per
10 individual dose, preferably of from about 1 to about 100 mg, most preferred of from about 1 to about 10 mg, are suitable for therapeutic treatments.

The active ingredient may be administered in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 $\mu\text{g/kg}$ i.v. and 1 $\mu\text{g/kg}$ p.o. The upper limit of the dosage range is presently considered
15 to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1 $\mu\text{g/kg}$ to about 10 mg/kg/day i.v., and from about 1 $\mu\text{g/kg}$ to about 100 mg/kg/day p.o.

Biological Activity

The compounds of the present invention are useful as blockers of chloride
20 channels, such as chloride channels of mast cells and basophils. For measuring the activity of the compounds, various in vitro and in vivo methods known in the art can be used.

Methods of Therapy

25 Compounds that are active as chloride channels blockers are likely to be useful in the treatment of a number of diseases, disorders and conditions, including diseases responsive to modulation of the mast cell or basophil activity, diseases responsive to inhibition of angiogenesis, and sickle cell anaemia.

Thus in a further aspect, the compounds of the invention are considered useful
30 for the treatment, prevention or alleviation of a disease, disorder or condition responsive to the blockade of chloride channels.

In a special embodiment, the disease or a disorder or a condition is responsive to modulation of the mast cell or basophil activity. In a further embodiment, the disease or a disorder or a condition is responsive to modulation of mast cell or basophil
35 production or secretion of histamine, neutral proteases or tryptases (such as chymotrypsins and carboxypeptidases), leukotrienes (such as LTC₄ and LTB₄), prostaglandins (such as PGD₂), TXA₂, PAF, or cytokines (such as IL-4 and TNF- α). In a further embodiment, the disorder or disease that is responsive to modulation of the mast cell or basophil activity is a disorder or disease that is responsive to modulation

of mast cell or basophil production or secretion of histamine. In a still further embodiment, the disorder or disease that is responsive to modulation of the mast cell or basophil activity is allergic bronchopulmonary aspergillosis (ABPA), allergic rhinitis, allergic skin disease, allergic skin reaction, drug induced allergic skin reaction,

5 anaphylaxis, asthma, atherosclerosis, atopic dermatitis (AD), bronchial asthma, cancer, chronic obstructive pulmonary disease (COPD), Chrohn's disease, contact dermatitis, dilated cardiomyopathy, fatal asthma, graft rejection, hypersensitivity pneumonitis, ischemic hearth disease, pulmonary fibrosis, rheumatoid arthritis, systemic sclerosis, urticaria, or uveoretinitis. In a special embodiment, the disorder or

10 disease that is responsive to modulation of the mast cell or basophil activity is allergic bronchopulmonary aspergillosis (ABPA), allergic rhinitis, allergic skin disease, allergic skin reaction, drug induced allergic skin reaction, asthma, bronchial asthma, fatal asthma or chronic obstructive pulmonary disease (COPD). In a further special embodiment, the disorder or disease is asthma, bronchial asthma, fatal asthma or

15 chronic obstructive pulmonary disease (COPD). In a further special embodiment, the disorder or disease is COPD. In a still further special embodiment, the disorder or disease is asthma.

In a further special embodiment, the disease or a disorder or a condition is responsive to inhibition of angiogenesis. In a special embodiment, the diseases,

20 disorders or conditions that are responsive to inhibition of angiogenesis are selected from:

- diseases, disorders or conditions that involve the proliferation of tumor cells, such as cancer, prostate cancer, lung cancer, breast cancer, bladder cancer, renal cancer, colon cancer, gastric cancer, pancreatic cancer, ovarian cancer,
- 25 melanoma, hepatoma, sarcoma and lymphoma;
- ophthalmic angiogenesis related diseases, disorders or conditions, such as exudative macular degeneration, age-related mucular degeneration, retinopathy, proliferative diabetic retinopathy, ischemic retinopathy (e.g. retinal vain or artery occlusion), retinopathy of prematurity, neovascular glaucoma, and
- 30 corneal neovascularization; and
- rheumatoid arthritis, and psoriasis.

In a special embodiment, the disease, disorder or condition to be treated is a preneoplastic disease state. In a further embodiment, the treatment is an anti-metastatic treatment. In a still further embodiment, the disease, disorder or condition

35 to be prevented is metastatic cancer.

In a still further embodiment, the disease, disorder or condition responsive to the blokade of chloride channels is sickle cell anaemia, brain oedema following ischaemia or tumors, diarrhea, hypertension, diuretic hypertension, glaucoma, or ulcers.

It is at present contemplated that suitable dosage ranges are 0.1 to 1000 milligrams daily, 10-500 milligrams daily, and especially 30-100 milligrams daily, dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject
5 involved and the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge. When administered in combination with compounds known in the art for treatment of the diseases, the dosing regimen may be reduced.

The treatment of the diseases and disorder can be in chronic or a long term
10 treatment as well as a treatment of sudden crisis in the disease and disorder.

EXAMPLES

The invention is further illustrated with reference to the following examples, which
15 are not intended to be in any way limiting to the scope of the invention as claimed.

Example 1

(2-Amino-phenyl)-phosphonic acid diethyl ester

20 Diethylphosphite (1.5 g, 11 mmol) in liquid ammonia (app. 100 ml) was added potassium tert.-butoxide (1.23 g, 11 mmol), the reaction mixture was stirred for 10 min. before 2-iodoaniline was added. The reaction mixture was irradiated (Hg-lamp) for an hour. Ammonia was evaporated and ammonium chloride was added with some ammonia, ammonia was evaporated off. The residue was added water and extracted
25 with dichloromethane. The title compound was purified by column chromatography. Yield 1.7 g (yellow oil).

Example 2

(2-Amino-5-bromo-phenyl)-phosphonic acid diethyl ester

30 (2-Amino-phenyl)-phosphonic acid diethyl ester (0.23g, 1 mmol) in glacial acetic acid (2 ml) under stirring was added bromine (0.16 g, 1 mmol, 1 eq.) in glacial acetic acid (2 ml) over 20 min. After the reaction was completed, the reaction mixture was poured into a saturated aqueous sodium bicarbonate solution. The title compound was extracted with dichloromethane and purified by column chromatography. Yield 0.23 g
35

Example 3

[(Dimethoxy-phosphoryl)-hydroxy-(2-nitro-phenyl)-methyl]-phosphonic acid dimethyl ester

Trimethyl phosphite (5.7 g, 45.7 mmol) was cooled to -10°C under a argon atmosphere and glacial acetic acid was added (1.44 ml), while keeping the temperature below 0°C , was drop wise added 2-nitrobenzoyl chloride, the reaction mixture was allowed to heat to room temperature and stirred for one hour. At a pressure of 10 mmHg was the reaction mixture heated to 40°C for one hour and cooled to room temperature. Ethyl acetate was added and the solution was washed with 5% sodium bicarbonate (aq.), the organic phase was dried and evaporated, the title compound was purified by column chromatography.

The following compound was made analogously;
[(Dimethoxy-phosphoryl)-hydroxy-(3-chloro-6-nitro-phenyl)-methyl]-phosphonic acid dimethyl ester.

15 Example 4

5-Amino-furan-2-carboxylic acid

5-Nitro-2-furoic acid methyl ester (14.3 g, 84 mmol) in ethyl acetate (110 ml) was added palladium on charcoal (0.75 g, 5 %), the solution was stirred at 40°C under a hydrogen atmosphere for 4 hours, the reaction mixture was filtered through celite, the title compound was isolated by evaporation and used as this in the next reaction.

Example 5

4-Amino-1-hydroxy-cyclohexa-2,4-dienecarboxylic acid methyl ester

5-Amino-furan-2-carboxylic acid (the crude product from example 4) was dissolved in benzene (0.5 L) and added acrylonitrile (200 ml), the reaction mixture was heated at reflux, stirred for 16 hours and evaporated, the residue was added toluene and evaporated. The title compound was crystallized from ethyl acetate, and used with out further purification in the next reaction.

Example 6

4-Amino-3-cyano-benzoic acid methyl ester

4-Amino-1-hydroxy-cyclohexa-2,4-dienecarboxylic acid methyl ester (the crude product from example 5) was dissolved in toluene (600 ml) and added boron trifluoride diethyl etherate (20 ml of 40 % in diethyl ether), the reaction mixture was added tetrahydrofurane (100 ml) and stirred at 85°C for 30 min. The reaction mixture was cooled to room temperature and poured into ice/water, the mixture was neutralized

with sodium hydroxide (1 M) and basified with saturated sodium bicarbonate. The layer was separated and the water phase was extracted with dichloro methane. The organic phases was dried and evaporated. The title compound was isolated from the residue by column chromatography. Yield 3.2 g.

5

Example 7**4-Amino-3-cyano-benzoic acid**

4-Amino-3-cyano-benzoic acid methyl ester (3.2 g, 10 mmol) in tetrahydrofurane/
10 water (110 ml, 1:1) was added lithium hydroxide hydrate (2.3 g, 30 mmol), the reaction mixture was stirred at room temperature for 20 hours and added hydro chloric acid (1 M) to pH = 3. From the mixture was tetrahydrofurane distilled of and the title compound precipitated out of solution.

15 **Example 8****4-Amino-3-cyano-N-methyl-benzamide**

4-Amino-3-cyano-benzoic acid (0.97 g, 6 mmol), benzotriazol-1-yloxytris-
(pyrrolidino)phosphonium hexafluorophosphate (3.3 g, 6.3 mmol) and
20 diisopropylethylamine (6 ml, 12 mmol) in anhydrous dimethyl formamide (25 ml) was added dimethylamine (6 ml of a 2 M in tetrahydrofurane), the reaction mixture was stirred at room temperature overnight. Some of the dimethylformamide was evaporated off, the crude product was dissolved in ethyl acetate (25 ml), washed with potassium hydrogen sulphate (twice with 0.5 M (25 ml)), sodium hydroxide (twice with
25 1 M (25 ml)), water (10 ml) and brine (25 ml). The organic layer was dried and evaporated, the title compound was isolated by column chromatography. Yield 0.39 g.

The following compounds were made analogously:

- 4-Amino-3-cyano-N,N-dimethyl-benzamide;
- 30 (4-Amino-3-cyano-benzoylamino)-acetic acid ethyl ester;
- 2-Amino-5-(piperidine-1-carbonyl)-benzonitrile;
- 4-Amino-3-cyano-N,N-diethyl-benzamide;
- [(4-Amino-3-cyano-benzoyl)-methyl-amino]-acetic acid.

Example 935 **(2-Amino-benzyl)-phosphonic acid dimethyl ester**

[(Dimethoxy-phosphoryl)-hydroxy-(2-nitro-phenyl)-methyl]-phosphonic acid dimethyl ester (4.7 g, 17.7 mmol) in 99 % ethyl alcohol (40 ml) was added Tin(II) chloride

dihydrate (14.4 g, 64 mmol, 5 eq.), the reaction mixture was heated at 70°C for 20 min. and poured into ice (250 ml), pH was adjusted to 7 with sodium hydroxide (1 M) and ethyl acetate was added, the emulsion was filtered through kieselguhr twice, the organic layer was washed with brine, dried, evaporated and the title compound was
5 isolated as an oil. Yield 2 g.

The following compound was made analogously:
(2-Amino-5-chloro-benzyl)-phosphonic acid dimethyl ester.

10 Example 10

2-Amino-benzeneboronic acid

2-Nitro-benzeneboronic acid (2.32 g, 14 mmol) in ethyl alcohol (130 ml, 99%) was added palladium on charcoal (0.232 g, 10 %), stirred under a hydrogen atmosphere (3
15 bar) overnight and filtered. The filtrate was evaporated, the title compound was crystallized from methyl alcohol and water. Yield 0.52 g.

Example 11

4-Methyl-phenyl-boronic acid

20

4-Bromo-toluene (50 g, 0.29 mol) in anhydrous diethyl ether (500 ml) was cooled to -20°C, while keeping the temperature under -20°C, was butyl lithium (127 ml of an 2.5 M solution in hexane 0.31 mol) added, after 15 min the solution was allowed to heat to 15°C and stirred at that temperature for an hour, then cooled to -55°C, while keeping
25 the temperature under -47°C was tributylborate (110 ml, 94 g, 0.41 mol, 1.4 eq.) added, the reaction mixture was allowed to heat to room temperature and stirred overnight. Hydrochloric acid (450 ml of 1 M) was added. The phases was separated, the water phase was extracted with diethyl ether, the organic phases was combined and extracted with sodium hydroxide (aq.) (300 ml + 2 times with 100ml of 2 M), the
30 water phases was added concentrated hydrochloric acid (app. 100 ml), the title compound precipitated and was isolated by filtration. Yield 32.6 g

Example 12

4-(Dihydroxyboryl) benzoic acid

35

4-Methyl-phenyl-boronic acid (32.6 g 0.24 mol) was dissolved in water (900 ml) containing sodium hydroxide (19.2 g 0.48 mol, 2 eq.) and added potassium permanganate (79.6 g, 0.5 mol, 2.1 eq.), the reaction mixture was stirred at room temperature for 72 hours and filtered, the precipitate was washed three times with

water (50 ml), the filtrate was added concentrated hydrochloric acid (app. 55 ml) and the title compound precipitated. Yield 34.5 g.

Example 13

5 4-(Dihydroxyboryl)-(N,N-dimethylbenzamide)

4-(Dihydroxyboryl) benzoic acid (34.4 g, 0.21 mol) was added to thionyl chloride (300 ml), the reaction mixture was heated at reflux overnight and evaporated to dryness, the residue was added dimethylamine (167 ml of a 40 % solution in water), the
10 reaction mixture was heated at reflux for 20 min. and filtered while still hot, the filtrate was cooled to room temperature and added concentrated hydrochloric acid and the title compound precipitated. Yield 25.1 g.

The following compounds were made analogously:

- 15 4-(Dihydroxyboryl)-benzamide;
[4-(Dihydroxyboryl)-benzoylamino]-acetic acid;
[4-(Dihydroxyboryl)-benzoyl-(N-methyl)-amino]-acetic acid.

Example 14

20 4'-Amino-3'-cyano-biphenyl-4-carboxylic acid dimethylamide

4-(Dihydroxyboryl)-(N,N-dimethylbenzamide) (1.2 g, 6.2 mmol), 2-amino-5-bromobenzonitrile (1.1 g, 5.6 mmol, 0.9 eq), potassium carbonate (2.3g, 16.9 mmol, 3.3 eq.), dimethoxyethylenglycol (20 ml) and water (10 ml) was mixed nitrogen was
25 bubbled through the mixture, bis(triphenylphosphine)palladium (II) chloride (0.05 g) was added, the reaction mixture was heated at reflux for 40 min, cooled to room temperature, added water (50 ml) and extracted with ethyl acetate (50 ml), the organic phase was washed with water (30 ml) dried, evaporated and the title compound was left as an oil. Yield 1.17 g.

30

Example 15

3-(4-Amino-3-cyano-phenyl)-acrylic acid methyl ester

2-Amino-5-bromo-benzonitrile (0.59 g 3 mmol), methylacrylate (0.52 g, 6 mmol) and
35 tri-o-tolylphosphine (0.49 mg, 0. 16 mmol) in anhydrous N,N-dimethyl formamide (5 ml) was added triethylamine (0.44 ml), the mixture was bubbled through with argon and palladium (II) acetate (4.5 mg, 0.02 mmol) and stirred at 120°C for 2.5 hours. Then the reaction was finished, the reaction mixture was cooled to room temperature and added hydrochloric acid (15 ml of 1 M), the title compound was extracted with

diethyl ether (four times with 25 ml), the organic phase was dried and evaporated.

The following compound was made analogously:
3-(4-Amino-3-cyano-phenyl)-acryl N,N-dimethyl amide.

5

Example 16**3-(4-Amino-3-cyano-phenyl)-propionic acid methyl ester**

3-(4-Amino-3-cyano-phenyl)-acrylic acid methyl ester (10 g, 49 mmol) and palladium
10 on charcoal (2 g, 10 %) in tetrahydrofuran (200 ml) was stirred vigorously under a
hydrogen atmosphere for 20 min., the reaction mixture was filtered through celite and
the title compound was isolated by filtration. Yield 10 g

The following compound was made analogously:

15 3-(4-Amino-3-cyano-phenyl)-propionic acid N,N-dimethyl amide.

Example 17**4'-Amino-3'-(1H-tetrazol-5-yl)-biphenyl-4-carboxylic acid dimethylamide**

20 4'-Amino-3'-cyano-biphenyl-4-carboxylic acid dimethylamide (1.15 g, 4.3 mmol) in
toluene (25 ml) was added sodium azide (0.42 g, 6.5 mmol, 1.5 eq.) and
triethylammonium chloride (0.9 g, 6.5 mmol, 1.5 eq.), the reaction mixture was stirred
at 60°C for 48 hours. The top phase was decanted from the bottom layer, the residue
was added water (25 ml), 96 % ethyl alcohol (25 ml) and concentrated hydro chloric
25 acid (app. 1 ml) and the title compound precipitated out. Yield 0.79 g.

The following compounds were made analogously:

4'-Amino-3-(1H-tetrazol-5-yl)-biphenyl-4-dimethyl-sulfon-amide;

2-Bromo-4-(1H-tetrazol-5-yl)-aniline;

30 2,6-Dibromo-4-(1H-tetrazol-5-yl)-aniline;

2-Bromo-5-(1H-tetrazol-5-yl)-aniline;

3-Chloro-6-(1H-tetrazol-5-yl)-aniline;

4-Bromo-2-(1H-tetrazol-5-yl)-aniline;

2,4-Dibromo-6-(1H-tetrazol-5-yl)-aniline;

35 [4'-Amino-3'-(1H-tetrazol-5-yl)-biphenyl-4-yl]-carbonyl-piperidin-1-yl;

2,4-Dichloro-6-(tetrazol-5-yl)-aniline;

4-Amino-N-methyl-3-(1H-tetrazol-5-yl)-benzamide;

[4-Amino-3-(1H-tetrazol-5-yl)-benzoylamino]-acetic acid;

3-[4-Amino-3-(1H-tetrazol-5-yl)-phenyl]-acrylic acid methyl ester;

- 3-[4-Amino-3-(1H-tetrazol-5-yl)-phenyl]-propionic acid methyl ester;
 N-[4-Amino-3-(1H-tetrazol-5-yl)-phenyl]-malonamic acid;
 3-[4-Amino-3-(1H-tetrazol-5-yl)-phenyl]-N,N-dimethyl-acrylamide;
 3-[4-amino-3-(1H-tetrazol-5-yl)-phenyl]-N-methyl-acrylamide;
 5 4-Amino-N,N-diethyl-3-(1H-tetrazol-5-yl)-benzamide;
 4-Amino-3-(1H-tetrazol-5-yl)-benzoyl-piperidin-1-yl;
 4'-Amino-3'-(1H-tetrazol-5-yl)-biphenyl-4-carboxylic acid amide;
 4-Amino-N,N-dimethyl-3-(1H-tetrazol-5-yl)-benzamide;
 [4-Amino-N-methyl-3-(1H-tetrazol-5-yl)-benzoylamino]-acetic acid;
 10 3-[4-Amino-3-(1H-tetrazol-5-yl)-phenyl]-N-methyl-propionamide;
 N-[4-Amino-3-(1H-tetrazol-5-yl)-phenyl]-benzamide.

Example 18

- N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4'-**
 15 **carboxylic acid dimethylamide] urea**

- 2'-Amino-3'-(1H-tetrazol-5-yl)-biphenyl-4-carboxylic acid dimethylamide (1 g, 3.2 mmol) in toluene (25 ml) was added 3,5-bis-(trifluoromethyl)-phenyl isocyanate (0.88 g, 3.3 mmol, app 1 eq.) and triethylamine (0.36 g, 3.6 mmol, 1.2 eq.), the reaction
 20 mixture was stirred overnight, an oil in the bottom of the flask was isolated. The oil was dissolved in 2-propanol (20 ml), the solution was added hydrochloric acid (1M) until pH = 2-3, the title compound precipitated. Yield 0.86 g. M.p. 222-224°C.

The following compounds were made analogously:

- 25 *N*-(3-Chloro-4-fluoro-phenyl)-*N'*-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4'-sulfonic acid-dimethylamide] urea; Mp. 240-243°C;
N-(4-Fluoro-3-trifluoromethyl-phenyl)-*N'*-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4'-sulfonic acid-dimethylamide] urea; Mp. 254-258°C;
N-(3-Fluoro-5-trifluoromethyl-phenyl)-*N'*-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4'-sulfonic
 30 acid-dimethylamide] urea; M.p. 255-256°C;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N'*-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4'-sulfonic acid-dimethylamide] urea; M.p. 203-205°C;
N-(3,5-Difluoro-phenyl)-*N'*-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4'-sulfonic acid-dimethylamide] urea; M.p. 254-255°C;
 35 *N*-(3,5-Dichloro-phenyl)-*N'*-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4'-carboxylic acid dimethylamide] urea; M.p. 201-204°C;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[2-bromo-4-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 229-233°C;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[2,6-dibromo-3-(1H-tetrazol-5-yl)-phenyl] urea;

- M.p. 220-222°C;
 4-Chloro-2-(3-cyclohexyl-ureido)-benzoic acid; M.p.
 N-Cyclohexyl-N'-(2,3-difluoro-4-trifluoromethyl-phenyl) urea;
 [3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid;
 5 1-(3,5-Bis-trifluoromethyl-phenylcarbamoyl)-pyrroline-2-carboxylic acid;
 1-(3,5-Bis-trifluoromethyl-phenylcarbamoyl)-4-hydroxy-pyrroline-2-carboxylic acid;
 N-Cyclohexyl-N'-(2,3-difluoro-phenyl) urea;
 N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[2-bromo-5-(1H-tetrazol-5-yl)-phenyl] urea;
 N-(Cyclohexyl)-N'-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
 10 5-Bromo-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]-benzoic acid;
 2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-cyclohexanecarboxylic acid;
 [3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-(5-trifluoromethyl-phenyl)-acetic acid;
 5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzoic acid;
 5-Bromo-2-[3-(3-bromo-phenyl)-ureido]-benzoic acid;
 15 N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
 N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
 [3-(4-Chloro-3-fluoro-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid;
 N-(3-Bromo-phenyl)-N'-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
 N-(3,5-Dichloro-phenyl)-N'-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
 20 N-(3-Chloro-phenyl)-N'-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
 [3-(3,5-Dichloro-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid;
 5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]-benzoic acid;
 5-Bromo-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]-benzoic acid;
 N-(3,5-Bis-trifluormethyl-phenyl)-N'-(phenyl-2-boronic acid) urea;
 25 N-(4-Chloro-3-fluoro-phenyl)-N'-(phenyl-2-boronic acid) urea;
 N-(3,5-Dichloro-phenyl)-N'-(phenyl-2-boronic acid) urea;
 N-Cyclohexyl-N'-(phenyl-2-boronic acid) urea;
 N-(2,6-Dichlooro-pyridin-4-yl)-N'-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 201-203°C;
 30 N-Cyclohexyl-N'-[4'-(N'',N''-dimethyl-1-carbonyl)-2-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea; M.p. 156-158°C;
 N-(2,6-Dichloro-pyridin-4-yl)-N'-[4'-(N'',N''-dimethyl-1-carbonyl)-2-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea; M.p. 163.8-164.5°C;
 N-Cyclohexyl-N'-[4-bromo-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 233-239°C;
 35 N-(2,6-Dichloro-pyridin-4-yl)-N'-[4-bromo-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 231-233°C;
 5-Chloro-2-[3-(pyridin-3-yl)-ureido]-benzoic acid; M.p. > 240°C;
 5-Bromo-2-[3-(pyridin-3-yl)-ureido]-benzoic acid; M.p. > 240°C;
 3,5-Dichloro-2-[3-(3,5-dichloro-phenyl)-ureido]-benzoic acid; M.p. 259-261°C;

- 3,5-Dichloro-2-[3-(3-chloro-4-fluoro-phenyl)-ureido]-benzoic acid; M.p. 174.5-175.9°C;
3,5-Dichloro-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]-benzoic acid; M.p. 199-200°C;
3,5-Dichloro-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzoic acid; M.p. 190.3-191.1°C;
- 5 3,5-Dichloro-2-[3-(4-fluoro-3-trifluoromethyl-phenyl)-ureido]-benzoic acid; M.p. 180-181°C;
3,5-Dichloro-2-[3-(3-fluoro-5-trifluoromethyl-phenyl)-ureido]-benzoic acid; M.p. 168-169°C;
3,5-Dichloro-2-[3-(3,5-difluoro-phenyl)-ureido]-benzoic acid; M.p. 245-249°C;
- 10 N-(4-Fluoro-3-trifluoromethyl-phenyl)-N'-[2,4-dibromo-6-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 195-196°C;
N-(3,4-Dichloro-phenyl)-N'-[2,4-dibromo-6-(1H-tetrazol-5-yl)-phenyl] urea; 201-203°C;
2-[3-(Thiophen-2-yl)-ureido]-benzoic acid;
2-[3-(Pyridin-4-yl)-ureido]-benzoic acid; M.p. > 230°C;
- 15 4-Chloro-2-[3-(pyridin-4-yl)-ureido]-benzoic acid; M.p. > 270°C;
5-Bromo-2-[3-(pyridin-4-yl)-ureido]-benzoic acid;
2-[3-(Pyridin-3-yl)-ureido]-nicotinic acid; M.p. > 220°C;
1-(4-Chloro-3-trifluoromethyl-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid; M.p. 159-161°C;
- 20 1-(3-Chloro-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid; M.p. 157-158°C;
1-(3-Bromo-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid; M.p. 176-177°C;
1-(3,5-Dichloro-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid; M.p. 180-181°C;
1-(Cyclohexyl-carbamoyl)-pyrrolidine-2-carboxylic acid; M.p. 172-174°C;
1-(2,6-Dichloro-pyridin-4-ylcarbamoyl)-pyrrolidine-2-carboxylic acid; M.p. 177-178°C;
- 25 2-[(3-(3-Chloro-phenyl)-ureido]-cyclohexanecarboxylic acid; M.p. 194-195°C;
2-[(3-(3-Bromo-phenyl)-ureido]-cyclohexanecarboxylic acid; M.p. 199-200°C;
2-[3-(3,5-Dichloro-phenyl)-ureido]-cyclohexanecarboxylic acid; M.p. 141-142°C;
2-(3-Cyclohexyl-ureido)-cyclohexanecarboxylic acid; M.p. 190-191°C;
2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-cyclohexane carboxylic acid; M.p. 199-200°C;
- 30 4-Chloro-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]-benzoic acid; M.p. 200-201°C;
5-Bromo-2-[3-(3-chloro-phenyl)-ureido]-benzoic acid; M.p. 194-195°C;
2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-nicotinic acid;
N-(2,3-Difluoro-4-trifluoromethyl-phenyl)-N'-(pyridin-3-yl) urea; M.p. 232-235°C;
N-[5-Chloro-2-(1H-tetrazol-5-yl)-phenyl]-N'-(pyridin-3-yl) urea; M.p. 214-220°C;
- 35 N-(Pyridin-3-yl)-N'-(2,3-difluoro-phenyl) urea; M.p. 211-215°C;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-(2,3-difluoro-4-trifluoromethyl-phenyl) urea; M.p. 194-195°C;
N-(2,6-Dichloro-pyridin-4-yl)-N'-(2,3-difluoro-4-trifluoromethyl-phenyl) urea; M.p. 210-211°C;

- N-[4-Bromo-2-(1H-tetrazol-5-yl)-phenyl]-N'-(pyridin-3-yl) urea; M.p. 193-194°C;
 2-[3-(Pyridin-3-yl)-ureido]-phenyl-boronic acid; M.p. 220-227°C;
 5-Bromo-2-(3-cyclohexyl-ureido)-benzoic acid; M.p. 178-179°C;
 [3-(3-Chloro-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid; M.p. 153-187°C;
 5 N-(2,3-Difluoro-4-trifluoromethyl-phenyl)-N'-(pyridin-4-yl) urea; M.p. 205-206°C;
 N-(2,3-Difluoro-phenyl)-N'-(pyridin-4-yl) urea; M.p. 201-215°C;
 2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-phenyl-boronic acid; M.p. 232-233°C;
 2-[3-(3-Bromo-phenyl)-ureido]-phenyl-dihydroxy-borane; M.p. 226-227°C;
 2-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]-cyclohexanecarboxylic acid; M.p. 213-
 10 214°C;
 2-[3-(3-Chloro-phenyl)-ureido]-cyclohexanecarboxylic acid; M.p. 173-178°C;
 2-[3-(3-Bromo-phenyl)-ureido]-cyclohexanecarboxylic acid; M.p. 175-223°C;
 2-[3-(2,6-Dichloro-phenyl)-ureido]-cyclohexanecarboxylic acid; M.p. 182-241°C;
 1-(4-Chloro-3-trifluoromethyl-phenylcarbamoyl)-4-hydroxy-pyrrolidine-2-carboxylic acid;
 15 M.p. 67-80°C;
 1-(3-Chloro-phenylcarbamoyl)-4-hydroxy-pyrrolidine-2-carboxylic acid; M.p. 156-
 157°C;
 1-(3-Bromo-phenylcarbamoyl)-4-hydroxy-pyrrolidine-2-carboxylic acid;
 1-(Pyridin-3-ylcarbamoyl)-pyrrolidine-2-carboxylic acid; M.p. 185-186°C;
 20 2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-cyclohexanecarboxylic acid; M.p. 168-197°C;
 4-Chloro-2-[3-(thiazol-2-yl)-ureido]-benzoic acid methyl ester;
 5-Bromo-2-[3-(pyridin-2-yl)-ureido]-benzoic acid methyl ester;
 4-Chloro-2-[3-(5-chloro-pyridin-2-yl)-ureido]benzoic acid;
 5-Bromo-2-(3-thiazol-2-yl-ureido)-benzoic acid methyl ester;
 25 2-[3-(5-Bromo-pyridin-3-yl)-ureido]-4-chloro-benzoic acid; M.p. >220°C;
 5-Bromo-2-[3-(pyridin-2-yl)-ureido]-benzoic acid;
 {2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
 {2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid;
 N-(3-Methoxy-phenyl)-N'-[4'-(N'',N''-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-
 30 biphenyl-4-yl] urea;
 N-(2-Methoxy-phenyl)-N'-[4'-(N'',N''-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-
 biphenyl-4-yl] urea;
 N-(4-Methoxy-phenyl)-N'-[4'-(N'',N''-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-
 biphenyl-4-yl] urea;
 35 N-(Naphthalen-1-yl)-N'-[4'-(N'',N''-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-
 4-yl] urea;
 N-(2-Trifluoromethyl-phenyl)-N'-[4'-(N'',N''-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-
 biphenyl-4-yl] urea;
 N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4'-(N'',N''-dimethyl-1-carbonyl)-3-(1H-

- tetrazol-5-yl)-biphenyl-4-yl] urea;
N-[2,4-Dibromo-6-(1H-tetrazol-5-yl)-phenyl]-N'-(2,6-dichloro-pyridin-4-yl) urea; M.p. 202-203°C;
N-(3,5-Dichloro-phenyl)-N'-[2,4-dibromo-6-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 221-
5 223°C;
3-Bromo-2-[3-(2H-1 λ ⁴-thiazol-2-yl)-ureido]-benzoic acid; M.p. >250°C;
{2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
M.p. 90-197°C;
{2-[3-(3-chloro-phenyl)-ureido]-phenyl}-phosphonic acid diethyl ester; M.p. oil;
10 {2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester; M.p. oil;
{2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester; M.p. 156-158°C;
{5-Bromo-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester; M.p. 152-158°C;
15 {5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester; M.p. oil;
{5-Bromo-2-[3-(3-chloro-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester; M.p. 160-207°C;
{5-Bromo-2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
20 M.p. 145-250°C;
{5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester; M.p. 139-144°C;
{5-Bromo-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]phenyl}-phosphonic acid diethyl ester;
2-[[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl]-phosphonic acid dimethyl
25 ester; M.p. 205-206°C;
2-[[3-(3,5-dichloro-phenyl)-ureido]-benzyl]-phosphonic acid dimethyl ester; M.p. 195-196°C;
2-[(3-Phenyl-ureido)-benzyl]-phosphonic acid dimethyl ester;
2-[3-(4-Chloro-phenyl)-ureido]-benzyl]-phosphonic acid dimethyl ester; M.p. 200-
30 202°C;
2-[[3-(3,4-Dichloro-phenyl)-ureido]-benzyl]-phosphonic acid dimethyl ester; M.p. 197-198°C;
{5-Chloro-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester; M.p. 210-211°C;
35 {5-Chloro-2-[3-(3,5-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester; M.p. 201-205°C;
[5-Chloro-2-(3-phenyl-ureido)-benzyl]-phosphonic acid dimethyl ester; M.p. 193-197°C;
{5-Chloro-2-[3-(3,4-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
{5-Chloro-2-[3-(3,4-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;

- M.p. 208-212°C;
2,5-Dichloro-3-[3-(3-bromo-phenyl)-ureido]-benzoic acid; M.p. 254-255°C;
2,5-Dichloro-3-[3-(3,5-dichloro-phenyl)-ureido]-benzoic acid; M.p. 256-257°C;
{2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-phenyl}-phosphonic acid diethyl ester; M.p.
5 166-167°C;
{2-[3-(2-Trifluoromethyl-phenyl)-ureido]-phenyl}-phosphonic acid diethyl ester; M.p. oil;
5-Chloro-2-[3-(1H-indol-2-yl)-ureido]-benzoic acid; M.p. > 200°C;
5-Bromo-2-[3-(1H-indol-2-yl)-ureido]-benzoic acid; M.p. > 230°C;
3-[3-(3-Bromo-phenyl)-ureido]-5-trifluoro-benzoic acid; M.p. 230-231°C;
10 3-[3-(3,5-Dichloro-phenyl)-ureido]-5-trifluoro-benzoic acid; M.p. 218-233°C;
3-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]-biphenyl-4-carboxylic acid amide; M.p.
210-211°C;
3-[3-(3,5-Dichloro-phenyl)-ureido]-biphenyl-4-carboxylic acid amide;
3-[3-(2,3-Dichloro-phenyl)-ureido]-biphenyl-4-carboxylic acid amide;
15 3-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-biphenyl-4-carboxylic acid amide;
4-[3-(3,5-Dichloro-phenyl)-ureido]-biphenyl-3-carboxylic acid;
4-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-biphenyl-3-carboxylic acid;
4-[3-(3,5-Difluoro-phenyl)-ureido]-biphenyl-3-carboxylic acid;
4-[3-(2-Chloro-phenyl)-ureido]-biphenyl-3-carboxylic acid;
20 N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4'-(piperidine-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(3,5-Dichloro-phenyl)-N'-[4'-(piperidine-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4'-(piperidine-1-carbonyl)-3-(1H-tetrazol-5-yl)-
25 biphenyl-4-yl] urea;
N-(3,5-Difluoro-phenyl)-N'-[4'-(piperidine-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(2-Chloro-phenyl)-N'-[4'-(piperidine-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
30 4-Chloro-2-[3-(5-phenyl-2H-pyrazol-3-yl)-ureido]-benzoic acid; M.p. > 270°C;
2-[3-(2-chloro-pyridin-3-yl)-ureido]-nicotinic acid; M.p. > 260°C;
4-Chloro-2-[3-(2-chloro-pyridin-3-yl)-ureido]-benzoic acid; M.p. > 215°C;
2-[3-(4-Chloro-phenyl)-ureido]-5-iodo-benzoic acid; M.p. > 200 °C;
5-Chloro-2-[3-(5-oxo-1-phenyl-pyrrolidin-3-yl)-ureido]-benzoic acid; M.p. > 240°C;
35 5-Bromo-2-(3-phenyl-ureido)-benzoic acid; M.p. > 200°C;
5-Bromo-2-[3-(2-fluoro-phenyl)-ureido]-benzoic acid; M.p. > 200°C;
5-Bromo-2-[3-(2-chloro-phenyl)-ureido]-benzoic acid; M.p. > 220°C;
5-Bromo-2-[3-(3,5-dimethyl-phenyl)-ureido]-benzoic acid; M.p. > 210°C;
5-Bromo-2-[3-(3,5-difluoro-phenyl)-ureido]-benzoic acid; M.p. 214-215°C;

- 5-Bromo-2-[3-(3,5-dimethoxy-phenyl)-ureido]-benzoic acid; M.p. 194-195°C;
N-(3,5-Dichloro-phenyl)-N'-[2,4-dichloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[2,4-dichloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
M.p. 205-207°C;
- 5 N-(3,5-Difluoro-phenyl)-N'-[2,4-dichloro-6-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 212-214°C;
5-Bromo-2-[3-(2,6-dichloro-phenyl)-ureido]-benzoic acid; M.p. > 225°C;
5-Bromo-2-[3-(2-bromo-phenyl)-ureido]-benzoic acid; M.p. > 225°C;
5-Bromo-2-[3-(4-chloro-3-nitro-phenyl)-ureido]-benzoic acid; M.p. > 230°C;
- 10 5-Bromo-2-[3-(4-butoxy-phenyl)-ureido]-benzoic acid; M.p. > 195°C;
5-Chloro-2-[3-(2-chloro-phenyl)-ureido]-benzoic acid; M.p. > 210°C;
5-Chloro-2-[3-(3,5-dimethyl-phenyl)-ureido]-benzoic acid; M.p. > 200°C;
2-[3-(4-Biphenyl)-ureido]-5-bromo-benzoic acid; M.p. > 200°C;
5-Chloro-2-[3-(3-iodo-phenyl)-ureido]-benzoic acid; M.p. > 210°C;
- 15 5-Chloro-2-(3-phenyl-ureido)-benzoic acid; M.p. > 195°C;
5-Chloro-2-[3-(2-fluoro-phenyl)-ureido]-benzoic acid; M.p. > 195°C;
N-(3,5-Bis-trifluoromethyl)-N'-[2,4-dichloro-5-(1H-tetrazol-5-yl)-phenyl] urea; M.p. > 200-203°C;
5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-nicotinic acid; M.p. > 300°C;
- 20 N-(3,5-Dichloro-phenyl)-N'-[4-(N''-methyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 276-277°C;
N-(3,5-Difluoro-phenyl)-N'-[4-(N''-methyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 277-278°C;
N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4-(carbonyl-amino-acetic acid)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 187-191°C;
- 25 N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4-(acrylic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 244-248°C;
N-(3,5-Dichloro-phenyl)-N'-[4-(acrylic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 237-245°C;
- 30 N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4-(acrylic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-N'-[4-(acrylic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 257-258°C;
N-(2-Chloro-phenyl)-N'-[4-(acrylic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea;
- 35 M.p. 184-185°C;
N-(4-Chloro-3-trifluoro-phenyl)-N'-[4-(propionic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 168-169°C;
N-(3,5-Dichloro-phenyl)-N'-[4-(propionic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 169-177°C;

- N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4-(propionic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 194-195°C;
N-(3,5-Difluoro-phenyl)-N'-[4-(propionic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 173-177°C;
- 5 N-(2-Chloro-phenyl)-N'-[4-(propionic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 228-229°C;
5-Bromo-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]-nicotinic acid; M.p. > 300°C;
N-(3,5-Dichloro-phenyl)-N'-[4-(N''-malonamic acid)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 223-225°C;
- 10 N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4-(N-malonamic acid)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 172-175°C;
N-(3,5-Difluoro-phenyl)-N'-[4-(N''-malonamic acid)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 170-173°C;
N-(2-Chloro-phenyl)-N'-[4-(N''-malonamic acid)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p.
- 15 158-160°C;
N-(3,5-Bis-trifluoromethyl-phenyl)-N'-{4-[(N'',N''-dimethyl)-acrylamide]-2-(1H-tetrazol-5-yl)-phenyl} urea;
N-(3,5-Difluoro-phenyl)-N'-{4-[(N'',N''-dimethyl)-acrylamide]-2-(1H-tetrazol-5-yl)-phenyl} urea;
- 20 N-(2-Chloro-phenyl)-N'-{4-[(N'',N''-dimethyl)-acrylamide]-2-(1H-tetrazol-5-yl)-phenyl} urea;
N-(3,5-Dichloro-phenyl)-N'-{4-[(N''-methyl)-acrylamide]-2-(1H-tetrazol-5-yl)-phenyl} urea;
N-(3,5-Difluoro-phenyl)-N'-{4-[(N''-methyl)-acrylamide]-2-(1H-tetrazol-5-yl)-phenyl}
- 25 urea;
N-(2-Chloro-phenyl)-N'-[4-(piperidine-1-carbonyl)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-N'-[4-(N'',N''-diethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4-(N'',N''-diethyl-carboxamide)-2-(1H-tetrazol-5-
- 30 yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-N'-[4-(N'',N''-diethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
N-(2-Chloro-phenyl)-N'-[4-(N'',N''-diethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 174-177°C;
- 35 N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4-(piperidine-1-carbonyl)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 210-212°C;
N-(3,5-dichloro-phenyl)-N'-[4-(piperidine-1-carbonyl)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 192-196°C;
N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4-(piperidine-1-carbonyl)-2-(1H-tetrazol-5-yl)-

- phenyl] urea; M.p. 189-190°C;
 N-(3,5-Difluoro-phenyl)-N'-[4-(piperidine-1-carbonyl)-2-(1H-tetrazol-5-yl)-phenyl] urea;
 M.p. 183-185°C;
 N-(3,5-Dichloro-phenyl)-N'-[4'-(carbonyl-(N''-methyl)amino-acetic acid)-2-(1H-tetrazol-
 5 5-yl)-4-biphenyl] urea; M.p. 286-287°C;
 N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4'-carboxamide-2-(1H-tetrazol-5-yl)-4-
 biphenyl] urea; M.p. 245-247°C;
 N-(3,5-Dichloro-phenyl)-N'-[4'-carboxamide-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
 N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4'-carboxamide-2-(1H-tetrazol-5-yl)-4-biphenyl]
 10 urea; M.p. 190-244°C;
 N-(3,5-Difluoro-phenyl)-N'-[4'-carboxamide-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
 N-(3,5-Dichloro-phenyl)-N'-[4-(N'',N''-dimethyl-caboxamide)-2-(1H-tetrazol-5-yl)-
 phenyl] urea; M.p. 184-244°C;
 N-(3,5-Difluoro-phenyl)-N'-[4-(N'',N''-dimethyl-caboxamide)-2-(1H-tetrazol-5-yl)-
 15 phenyl] urea; M.p. 183-198°C;
 N-(4-Chloro-3-trifluoromethyl)-N'-[4-(N'',N''-diethyl-carboxamide)-2-(1H-tetrazol-5-yl)-
 phenyl] urea; M.p. 191-240°C;
 N-(3,5-Dichloro-phenyl)-N'-[4'-(carbonyl-amino-acetic acid)-2-(1H-tetrazol-5-yl)-4-
 biphenyl] urea; M.p. 265-266°C;
 20 N-(3,5-Difluoro-phenyl)-N'-[4'-(carbonyl-amino-acetic acid)-2-(1H-tetrazol-5-yl)-4-
 biphenyl] urea; M.p. 235-242°C;
 N-(2-Chloro-phenyl)-N'-[4'-(carbonyl-amino-acetic acid)-2-(1H-tetrazol-5-yl)-4-
 biphenyl] urea; M.p. 253-254°C;
 N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4'-[carbonyl-(N''-methyl)-amino-acetic acid]-
 25 2-(1H-tetrazol-5-yl)-4-biphenyl] urea; M.p. 249-250°C;
 N-(3,5-Dichloro-phenyl)-N'-[4'-[carbonyl-(N''-methyl)-amino-acetic acid]-2-(1H-
 tetrazol-5-yl)-4-biphenyl] urea; M.p. 251-286°C;
 N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4'-[carbonyl-(N''-methyl)-amino-acetic acid]-2-
 (1H-tetrazol-5-yl)-4-biphenyl] urea; M.p. 190-191°C;
 30 N-(3,5-Difluoro-phenyl)-N'-[4'-(carbonyl-amino-acetic acid)-2-(1H-tetrazol-5-yl)-4-
 biphenyl] urea; M.p. decomp.;
 N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4-(N''-methyl-propylamide)-2-(1H-tetrazol-5-
 yl)-phenyl] urea;
 N-(3,5-Dichloro-phenyl)-N'-[4-(N''-methyl-propylamide)-2-(1H-tetrazol-5-yl)-phenyl]
 35 urea;
 N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4-(N''-methyl-propylamide)-2-(1H-tetrazol-5-yl)-
 phenyl] urea;
 N-(3,5-Difluoro-phenyl)-N'-[4-(N''-methyl-propylamide)-2-(1H-tetrazol-5-yl)-phenyl]
 urea;

- N-(2-chloro-phenyl)-N'-[4-(N''-methyl-propylamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
 5-Chloro-2-[3-(3,5-difluoro-phenyl)-ureido]-benzoic acid;
 5-Chloro-2-[3-(3,5-dimethoxy-phenyl)-ureido]-benzoic acid;
 5-Chloro-2-[3,4-dichloro-phenyl)-ureido]-benzoic acid;
 5 2-[3-(4-Butoxy-phenyl)-ureido]-5-chloro- benzoic acid;
 5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]-nicotinic acid; M.p > 300°C;
 5-Bromo-2-[3-(3,5-difluoro-phenyl)-ureido]-nicotinic acid; M.p > 300°C;
 N-(2,6-Dichloro-phenyl)-N'-[2,4-dichloro-6-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 214-215°C;
 10 N-(2,4,6-trichloro-phenyl)-N'-[2,4-dichloro-6-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 207-209°C;
 5-Bromo-2-[3-(2,4,6-trichloro-phenyl)-ureido]-nicotinic acid; M.p. > 300°C;
 N-(3,5-Dichloro-phenyl)-N'-[4-benzamide-2-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
 M.p. 238-239°C;
 15 N-(3,5-Difluoro-phenyl)-N'-[4-benzamide-2-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
 M.p. 254-256°C;
 N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4-benzamide-2-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 250-253°C;
 N-(4-Chloro-3-trifluoromethyl-phenyl)- N'-[4-benzamide-2-(1H-tetrazol-5-yl)-phenyl)
 20 urea; M.p. 248-250°C;
 5-Chloro-2-[3-(2,6-dichloro-phenyl)-ureido]-benzoic acid. M.p. > 300°C;
 N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4'-(N''-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea; M.p. 244-245°C;
 N-(4-Chloro-3-trifluoromethyl-phenyl)- N'-[4-(N'',N''-dimethyl acryl-amide)-2-(1-H-tetrazol-5-yl)-phenyl] urea; M.p. 169-171°C;
 25 N-(3,5-dichloro-phenyl)-N'-[4-(N'',N''-dimethyl acryl-amide)-2-(1-H-tetrazol-5-yl)phenyl] urea; M.p. 190-193°C;
 N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4'-(N''-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea; M.p. 275-296°C;

30

Example 19**3,5-Bis-[3-(3-bromo-phenyl)-ureido]- benzoic acid**

- 3,5-Diaminobenzoic acid (152 mg, 1 mmol) in anhydrous acetonitrile (5 ml) under an
 35 argon atmosphere was added 3-bromophenyl isocyanate (396 mg, 2 mmol, 2 eq.).
 The reaction mixture was stirred at 60 °C for 16 hours. The title compound precipitated out of solution and was isolated by filtration. Yield 377 mg. M.p. > 300°C.

The following compounds were made analogously:

3,5-Bis-[3-(3,5-dichloro-phenyl)-ureido]- benzoic acid; M.p. > 300°C;
 3,5-Bis-[3-(3,5-difluoro-phenyl)-ureido]- benzoic acid; M.p. > 300°C;
 3,5-Bis-[3-(3,5-bis-trifluoromethylphenyl)-ureido]- benzoic acid; M.p. > 300°C.

Example 20

5 {2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid

{2-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]-phenyl}-phosphonic acid diethyl ester (400 mg, 0.8 mmol) was dissolved in anhydrous dichloromethane (3 ml). Under a argon atmosphere was added trimethylsilyl bromide (2 ml, 15 mmol, 19 eq.), the
 10 reaction mixture was heated at reflux overnight then evaporated to dryness, to the residue was added water (10 ml) and ethyl acetate (10 ml), the organic layer was separated, dried and evaporated. The title compound was crystallized from dichloromethane. Yield 340 mg, M.p. 153-157°C.

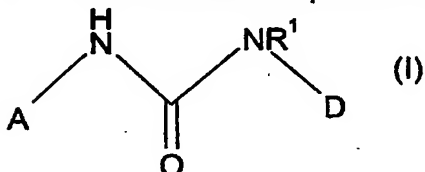
15 The following compounds were made analogously:

- {2-[3-(3-chloro-phenyl)-ureido]phenyl}-phosphonic acid; M.p. 147-149°C;
- {2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid; M.p. 145-151°C;
- {2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid; M.p. 167-170°C;
- {5-Bromo-2-[3-(3,5 bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid; M.p.
 20 150-153°C;
- {5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid; M.p. 267-273°C;
- {5-Bromo-2-[3-(3-chloro-phenyl)-ureido]phenyl}-phosphonic acid; M.p. 160-207°C;
- {5-Bromo-2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid; M.p. 204-210°C;
- 25 {5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid; M.p. 212-288°C;
- {5-Bromo-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]phenyl}-phosphonic acid;
- 2-[[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl]-phosphonic acid; M.p. 185-197°C;
- 2-[[3-(3,5-Dichloro-phenyl)-ureido]-benzyl]-phosphonic acid; M.p. 192-193°C;
- 30 2-[[3-(3-Phenyl-ureido)-benzyl]-phosphonic acid; M.p. 166-168°C;
- 2-[3-(4-Chloro-phenyl)-ureido]-benzyl]-phosphonic acid; M.p. 184-191°C;
- 2-[[3-(3,4-Dichloro-phenyl)-ureido]-benzyl]-phosphonic acid; M.p. 177-178°C;
- {5-Chloro-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl}-phosphonic acid; M.p. 177-180°C;
- 35 {5-Chloro-2-[3-(3,5-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid; Mp. 181-182°C;
- [5-Chloro-2-(3-phenyl-ureido)-benzyl]-phosphonic acid; M.p. 174-182°C;
- {5-Chloro-2-[3-(4-chloro-phenyl)-ureido]-benzyl}-phosphonic acid; M.p. 189-190°C;
- {5-Chloro-2-[3-(3,4-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid; M.p. 191-192°C;

{2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-phenyl}-phosphonic acid; M.p. 185-189°C;
{2-[3-(2-Trifluoromethyl-phenyl)-ureido]-phenyl}-phosphonic acid; M.p. 155-162°C.

CLAIMS:

1. A chemical compound represented by general formula (I)



- 5 or a pharmaceutically acceptable salt thereof, wherein

A represents a ring system selected from the group consisting of:

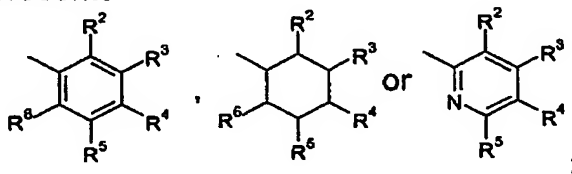
cyclohexanyl, phenyl, pyridyl, thienyl, thiazolyl, naphthyl, indolyl, pyrazolyl and oxo-pyrrolidinyl;

- 10 which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:

halogen, trifluoromethyl, nitro, alkyl, alkoxy, and phenyl; and

R¹ represents -H; and

- 15 D represents



wherein

one of R², R³, and R⁴ is selected from the group consisting of:

tetrazolyl, -COOR^a, -B(OH)₂, -PO(OR^a)₂, -CH₂-PO(OR^a)₂, and -CONH;

- 20 wherein R^a is hydrogen or alkyl;

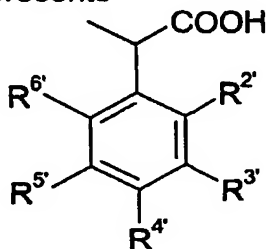
or R² and R³ or R³ and R⁴ both represent fluoro; and

R⁵, R⁶ and the remaining one or two of R², R³ and R⁴ independently of each other represent:

- hydrogen, halogen, trifluoromethyl,
- 25 ○ -CH=CH-COOR^b, -CH₂-CH₂-COOR^b,
- -CO-NR^b-CH₂-COOR^c; -CO-NR^bR^c,
- -CH=CH-CO-NR^bR^c; -CH₂-CH₂-CO-NR^bR^c,
- piperidylcarbonyl,
- -NH-CO-R^d or -NH-CO-NH-R^d;
- 30 wherein R^d is phenyl optionally substituted with one or more substituents independently selected from halogen or trifluoromethyl; or

- phenyl optionally substituted with
 $-\text{SO}_2-\text{NR}^b\text{R}^c$, $-\text{CO}-\text{NR}^b\text{R}^c$, $-\text{CO}-\text{NR}^b-\text{CH}_2-\text{COOR}^c$, or piperidylcarbonyl;
 wherein R^b and R^c independently are hydrogen or alkyl;

- 5 or R^1 represents $-\text{H}$; and
 D represents

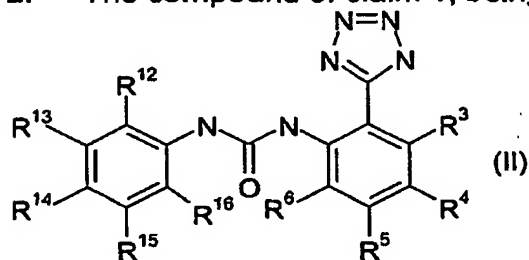


wherein $\text{R}^{2'}$, $\text{R}^{3'}$, $\text{R}^{4'}$, $\text{R}^{5'}$, $\text{R}^{6'}$ independently of each other represent hydrogen, halogen, or trifluoromethyl:

10

- or R^1 together with D forms $-\text{CHR}^e-\text{CH}_2-\text{CHR}^f-\text{CH}_2-$;
 wherein R^e represents $-\text{COOH}$;
 R^f represents hydrogen or hydroxy.

- 15 2. The compound of claim 1, being a compound of general formula (II)



or a pharmaceutically acceptable salt thereof, wherein

R^3 , R^4 , R^5 and R^6 independently of each other represent:

20

- hydrogen, halogen, trifluoromethyl,
- $-\text{CH}=\text{CH}-\text{COOR}^b$, $-\text{CH}_2-\text{CH}_2-\text{COOR}^b$,
- $-\text{CO}-\text{NR}^b-\text{CH}_2-\text{COOR}^c$; $-\text{CO}-\text{NR}^b\text{R}^c$,
- $-\text{CH}=\text{CH}-\text{CO}-\text{NR}^b\text{R}^c$; $-\text{CH}_2-\text{CH}_2-\text{CO}-\text{NR}^b\text{R}^c$,
- piperidylcarbonyl,

25

- $-\text{NH}-\text{CO}-\text{R}^d$ or $-\text{NH}-\text{CO}-\text{NH}-\text{R}^d$;

wherein R^d is phenyl optionally substituted with one or more substituents independently selected from halogen or trifluoromethyl (bromo, dichloro); or

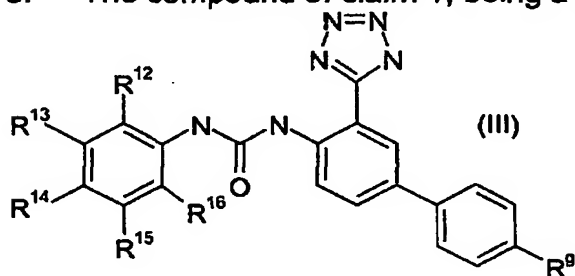
- phenyl optionally substituted with

$-\text{SO}_2-\text{NR}^b\text{R}^c$, $-\text{CO}-\text{NR}^b\text{R}^c$, $-\text{CO}-\text{NR}^b-\text{CH}_2-\text{COOR}^c$, or piperidylcarbonyl;
wherein R^b and R^c independently are hydrogen or alkyl;

R^{12} , R^{13} , R^{14} , R^{15} , and R^{16} independently of each other represent

5 hydrogen, halogen, trifluoromethyl, nitro, alkyl, or alkoxy.

3. The compound of claim 1, being a compound of general formula (III)



or a pharmaceutically acceptable salt thereof, wherein

10

R^9 represents $-\text{CO}-\text{NR}^b\text{R}^c$, $-\text{CO}-\text{NR}^b-\text{CH}_2-\text{COOR}^c$, or piperidylcarbonyl;
wherein R^b and R^c independently are hydrogen or alkyl;

two of R^{12} , R^{13} , R^{14} , R^{15} , and R^{16} independently of each other represent

15 halogen, trifluoromethyl, nitro, alkyl, or alkoxy;

and the remaining three of R^{12} , R^{13} , R^{14} , R^{15} , and R^{16} represent hydrogen.

4. The formula of claim 1, wherein

A represents a ring system selected from the group consisting of:

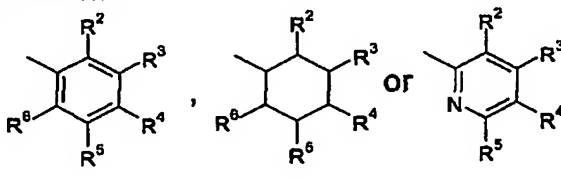
20 cyclohexanyl, phenyl, pyridyl, thienyl, thiazolyl, and pyrazolyl;

which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:

halogen, trifluoromethyl, nitro, alkyl, alkoxy, and phenyl; and

R^1 represents $-\text{H}$; and

25 D represents



wherein

R^2 represents $-\text{COOR}^a$;

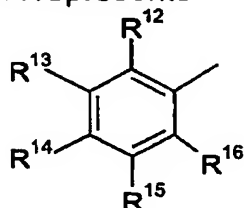
wherein R^a is hydrogen or alkyl;

30 R^3 , R^4 , R^5 , and R^6 independently of each other represent:

- hydrogen, halogen, trifluoromethyl,
- $-\text{NH}-\text{CO}-\text{R}^d$ or $-\text{NH}-\text{CO}-\text{NH}-\text{R}^d$;
wherein R^d is phenyl optionally substituted with one or more substituents independently selected from halogen or trifluoromethyl; or
- 5 ○ phenyl optionally substituted with
 $-\text{SO}_2-\text{NR}^b\text{R}^c$, $-\text{CO}-\text{NR}^b\text{R}^c$, $-\text{CO}-\text{NR}^b-\text{CH}_2-\text{COOR}^c$, or piperidylcarbonyl;
wherein R^b and R^c independently are hydrogen or alkyl.

5. The compound of claim 4, wherein

10 A represents



wherein R^{12} , R^{13} , R^{14} , R^{15} , and R^{16} independently of each other represent:
halogen, trifluoromethyl, nitro, alkyl, alkoxy, or phenyl.

15 6. The compound of claim 1, wherein

A represents a ring system selected from the group consisting of:

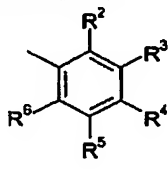
cyclohexanyl, phenyl, and pyridyl;

which ring system is optionally substituted with one or more substituents independently
selected from the group consisting of:

20 halogen, trifluoromethyl, nitro, alkyl, and alkoxy; and

R^1 represents $-\text{H}$; and

D represents



25 wherein

R^2 represents $-\text{B}(\text{OH})_2$, $-\text{PO}(\text{OR}^a)_2$, $-\text{CH}_2-\text{PO}(\text{OR}^a)_2$, or $-\text{CONH}$;

wherein R^a is hydrogen or alkyl (hydrogen, methyl, ethyl);

R^2 , R^3 , R^4 , R^5 , and R^6 independently of each other represent:
hydrogen, halogen, trifluoromethyl, or phenyl.

30

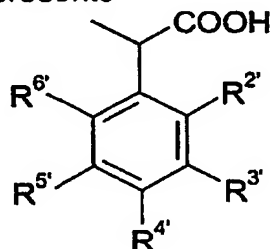
7. The compound of claim 1, wherein

A represents phenyl optionally substituted with one or more substituents independently selected from the group consisting of:

halogen, trifluoromethyl, nitro, alkyl, and alkoxy; and

5 R^1 represents -H; and

D represents



wherein $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, $R^{6'}$ independently of each other represent hydrogen, halogen, or trifluoromethyl.

10

8. The compound of claim 1, wherein

A represents a ring system selected from the group consisting of:

cyclohexanyl, phenyl, and pyridyl;

which ring system is optionally substituted with one or more substituents independently

15 selected from the group consisting of:

halogen, trifluoromethyl, nitro, alkyl, and alkoxy; and

R^1 together with D forms $-\text{CHR}^e-\text{CH}_2-\text{CHR}^f-\text{CH}_2-$;

wherein R^e represents $-\text{COOH}$;

R^f represents hydrogen or hydroxy.

20

9. The compound of claim 1, wherein

A represents a ring system selected from the group consisting of:

cyclohexanyl, phenyl, and pyridyl;

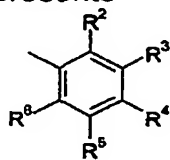
which ring system is optionally substituted with one or more substituents independently

25 selected from the group consisting of:

halogen, trifluoromethyl, nitro, alkyl, and alkoxy;

R^1 represents -H; and

D represents



30 wherein

R^2 and R^3 or R^3 and R^4 both represent fluoro; and
 R^5 , R^6 and the remaining one or two of R^2 , R^3 and R^4 independently of each other
 represent hydrogen, halogen, or trifluoromethyl.

5 10. The compound of claim 1, wherein

A represents a ring system selected from the group consisting of:

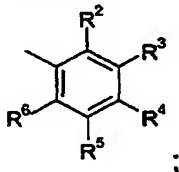
cyclohexanyl, pyridyl, and naphthyl;

which ring system is optionally substituted with one or more substituents independently
 selected from the group consisting of:

10 halogen, trifluoromethyl, nitro, alkyl, and alkoxy; and

R^1 represents -H; and

D represents



15 wherein

R^2 represents tetrazolyl;

R^3 , R^4 , R^5 , and R^6 independently of each other represent:

o hydrogen, halogen, trifluoromethyl; or

o phenyl substituted with

20 $-SO_2-NR^bR^c$, $-CO-NR^bR^c$, $-CO-NR^b-CH_2-COOR^c$, or piperidylcarbonyl;

wherein R^b and R^c independently are hydrogen or alkyl (methyl).

11. The compound of claim 1, being

N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[2-bromo-4-(1H-tetrazol-5-yl)-phenyl] urea;

25 N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[2,6-dibromo-3-(1H-tetrazol-5-yl)-phenyl] urea;

N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[2-bromo-5-(1H-tetrazol-5-yl)-phenyl] urea;

5-Chloro-2-[3-(1H-indol-2-yl)-ureido]-benzoic acid;

5-Bromo-2-[3-(1H-indol-2-yl)-ureido]-benzoic acid;

N-(3-Fluoro-5-trifluoromethyl-phenyl)-N'-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4'-sulfonic

30 acid-dimethylamide] urea;

N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4'-sulfonic
 acid-dimethylamide] urea;

- N-(3,5-Difluoro-phenyl)-N'-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4'-sulfonic acid-dimethylamide] urea;
- N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
- N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
- 5 N-(3-Bromo-phenyl)-N'-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
- N-(3,5-Dichloro-phenyl)-N'-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
- N-(3-Chloro-phenyl)-N'-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
- N-(4-Fluoro-3-trifluoromethyl-phenyl)-N'-[2,4-dibromo-6-(1H-tetrazol-5-yl)-phenyl] urea;
- N-(3,4-Dichloro-phenyl)-N'-[2,4-dibromo-6-(1H-tetrazol-5-yl)-phenyl] urea;
- 10 N-(3-Methoxy-phenyl)-N'-[4'-(N'',N''-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
- N-(2-Methoxy-phenyl)-N'-[4'-(N'',N''-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
- N-(4-Methoxy-phenyl)-N'-[4'-(N'',N''-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-
- 15 biphenyl-4-yl] urea;
- N-(2-Trifluoromethyl-phenyl)-N'-[4'-(N'',N''-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
- N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4'-(N'',N''-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
- 20 N-(3,5-Dichloro-phenyl)-N'-[2,4-dibromo-6-(1H-tetrazol-5-yl)-phenyl] urea;
- N-(2-Chloro-phenyl)-N'-[4'-(piperidine-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
- N-(3,5-Dichloro-phenyl)-N'-[2,4-dichloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
- N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[2,4-dichloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
- 25 N-(3,5-Difluoro-phenyl)-N'-[2,4-dichloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
- N-(3,5-Bis-trifluoromethyl)-N'-[2,4-dichloro-5-(1H-tetrazol-5-yl)-phenyl] urea;
- N-(3,5-Dichloro-phenyl)-N'-[4-(N''-methyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
- N-(3,5-Difluoro-phenyl)-N'-[4-(N''-methyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl]
- 30 urea;
- N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4-(carbonyl-amino-acetic acid)-2-(1H-tetrazol-5-yl)-phenyl] urea;
- N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4-(acrylic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea;
- 35 N-(3,5-Dichloro-phenyl)-N'-[4-(acrylic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea;
- N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4-(acrylic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea;
- N-(3,5-Difluoro-phenyl)-N'-[4-(acrylic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl]

urea;

N-(2-Chloro-phenyl)-N'-[4-(acrylic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea;

N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4-(propionic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea;

5 N-(3,5-Dichloro-phenyl)-N'-[4-(propionic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea;

N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4-(propionic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea;

N-(3,5-Difluoro-phenyl)-N'-[4-(propionic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl]

10 urea;

N-(2-Chloro-phenyl)-N'-[4-(propionic acid methyl ester)-2-(1H-tetrazol-5-yl)-phenyl] urea;

N-(3,5-Dichloro-phenyl)-N'-[4-(N''-malonamic acid)-2-(1H-tetrazol-5-yl)-phenyl] urea;

N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4-(N-malonamic acid)-2-(1H-tetrazol-5-yl)-

15 phenyl] urea;

N-(3,5-Difluoro-phenyl)-N'-[4-(N''-malonamic acid)-2-(1H-tetrazol-5-yl)-phenyl] urea;

N-(2-Chloro-phenyl)-N'-[4-(N''-malonamic acid)-2-(1H-tetrazol-5-yl)-phenyl] urea; M.p. 158-160°C;

N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4-[(N'',N''-dimethyl)-acrylamide]-2-(1H-tetrazol-5-yl)-phenyl] urea;

20

N-(3,5-Difluoro-phenyl)-N'-[4-[(N'',N''-dimethyl)-acrylamide]-2-(1H-tetrazol-5-yl)-phenyl] urea;

N-(2-Chloro-phenyl)-N'-[4-[(N'',N''-dimethyl)-acrylamide]-2-(1H-tetrazol-5-yl)-phenyl] urea;

25 N-(3,5-Dichloro-phenyl)-N'-[4-[(N''-methyl)-acrylamide]-2-(1H-tetrazol-5-yl)-phenyl] urea;

N-(3,5-Difluoro-phenyl)-N'-[4-[(N''-methyl)-acrylamide]-2-(1H-tetrazol-5-yl)-phenyl] urea;

N-(2-Chloro-phenyl)-N'-[4-(piperidine-1-carbonyl)-2-(1H-tetrazol-5-yl)-phenyl] urea;

30 N-(3,5-Dichloro-phenyl)-N'-[4-(N'',N''-diethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;

N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4-(N'',N''-diethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;

N-(3,5-Difluoro-phenyl)-N'-[4-(N'',N''-diethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;

35

N-(2-Chloro-phenyl)-N'-[4-(N'',N''-diethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;

N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4-(piperidine-1-carbonyl)-2-(1H-tetrazol-5-yl)-phenyl] urea;

- N-(3,5-dichloro-phenyl)-N'-[4-(piperidine-1-carbonyl)-2-(1H-tetrazol-5-yl)-phenyl] urea;
 N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4-(piperidine-1-carbonyl)-2-(1H-tetrazol-5-yl)-phenyl] urea;
 N-(3,5-Difluoro-phenyl)-N'-[4-(piperidine-1-carbonyl)-2-(1H-tetrazol-5-yl)-phenyl] urea;
- 5 N-(3,5-Dichloro-phenyl)-N'-[4'-(carbonyl-(N''-methyl)amino-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
 N-(3,5-Dichloro-phenyl)-N'-[4-(N'',N''-dimethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
 N-(3,5-Difluoro-phenyl)-N'-[4-(N'',N''-dimethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
- 10 N-(4-Chloro-3-trifluoromethyl)-N'-[4-(N'',N''-diethyl-carboxamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
 N-(2-Chloro-phenyl)-N'-[4'-(carbonyl-amino-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
- 15 N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4-(N''-methyl-propylamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
 N-(3,5-Dichloro-phenyl)-N'-[4-(N''-methyl-propylamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
 N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4-(N''-methyl-propylamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
- 20 N-(3,5-Difluoro-phenyl)-N'-[4-(N''-methyl-propylamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
 N-(2-chloro-phenyl)-N'-[4-(N''-methyl-propylamide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
 N-(2,6-Dichloro-phenyl)-N'-[2,4-dichloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
- 25 N-(2,4,6-trichloro-phenyl)-N'-[2,4-dichloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
 N-(3,5-Dichloro-phenyl)-N'-[4-benzamide-2-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
 N-(3,5-Difluoro-phenyl)-N'-[4-benzamide-2-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
 N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4-benzamide-2-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
- 30 N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4-benzamide-2-(1H-tetrazol-5-yl)-phenyl] urea;
 N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4-(N'',N''-dimethyl acryl-amide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
 N-(3,5-dichloro-phenyl)-N'-[4-(N'',N''-dimethyl acryl-amide)-2-(1H-tetrazol-5-yl)-phenyl] urea;
- 35 N-(3-Chloro-4-fluoro-phenyl)-N'-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4'-sulfonic acid-dimethylamide] urea;
 N-(4-Fluoro-3-trifluoromethyl-phenyl)-N'-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4'-sulfonic acid-dimethylamide] urea;

- N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4'-carboxylic acid dimethylamide] urea
- N-(3,5-Dichloro-phenyl)-N'-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4'-carboxylic acid dimethylamide] urea;
- 5 N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4'-(piperidine-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
- N-(3,5-Dichloro-phenyl)-N'-[4'-(piperidine-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
- N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4'-(piperidine-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
- 10 N-(3,5-Difluoro-phenyl)-N'-[4'-(piperidine-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
- N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4'-carboxamide-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
- 15 N-(3,5-Dichloro-phenyl)-N'-[4'-carboxamide-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
- N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4'-carboxamide-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
- N-(3,5-Difluoro-phenyl)-N'-[4'-carboxamide-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
- N-(3,5-Dichloro-phenyl)-N'-[4'-(carbonyl-amino-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
- 20 N-(3,5-Difluoro-phenyl)-N'-[4'-(carbonyl-amino-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
- N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4'-[carbonyl-(N''-methyl)-amino-acetic acid]-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
- 25 N-(3,5-Dichloro-phenyl)-N'-[4'-[carbonyl-(N''-methyl)-amino-acetic acid]-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
- N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4'-[carbonyl-(N''-methyl)-amino-acetic acid]-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
- N-(3,5-Difluoro-phenyl)-N'-[4'-(carbonyl-amino-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
- 30 N-(3,5-Bis-trifluoromethyl-phenyl)-N'-[4'-(N''-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
- N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4'-(N''-acetic acid)-2-(1H-tetrazol-5-yl)-4-biphenyl] urea;
- 35 4-Chloro-2-(3-cyclohexyl-ureido)-benzoic acid;
- 5-Bromo-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]-benzoic acid;

- 2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-cyclohexanecarboxylic acid;
5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3-bromo-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]-benzoic acid;
5 5-Bromo-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]-benzoic acid;
N-(3,5-Bis-trifluoromethyl-phenyl)-N'-(phenyl-2-boronic acid) urea;
N-(4-Chloro-3-fluoro-phenyl)-N'-(phenyl-2-boronic acid) urea;
N-(3,5-Dichloro-phenyl)-N'-(phenyl-2-boronic acid) urea;
N-Cyclohexyl-N'-(phenyl-2-boronic acid) urea;
10 5-Chloro-2-[3-(pyridin-3-yl)-ureido]-benzoic acid;
5-Bromo-2-[3-(pyridin-3-yl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(3,5-dichloro-phenyl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(3-chloro-4-fluoro-phenyl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]-benzoic acid;
15 3,5-Dichloro-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(4-fluoro-3-trifluoromethyl-phenyl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(3-fluoro-5-trifluoromethyl-phenyl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(3,5-difluoro-phenyl)-ureido]-benzoic acid;
2-[3-(Thiophen-2-yl)-ureido]-benzoic acid;
20 2-[3-(Pyridin-4-yl)-ureido]-benzoic acid;
4-Chloro-2-[3-(pyridin-4-yl)-ureido]-benzoic acid;
5-Bromo-2-[3-(pyridin-4-yl)-ureido]-benzoic acid;
2-[3-(Pyridin-3-yl)-ureido]-nicotinic acid;
2-[(3-(3-Chloro-phenyl)-ureido]-cyclohexanecarboxylic acid;
25 2-[(3-(3-Bromo-phenyl)-ureido]-cyclohexanecarboxylic acid;
2-[3-(3,5-Dichloro-phenyl)-ureido]-cyclohexanecarboxylic acid;
2-(3-Cyclohexyl-ureido)-cyclohexanecarboxylic acid;
2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-cyclohexane carboxylic acid;
4-Chloro-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]-benzoic acid;
30 5-Bromo-2-[3-(3-chloro-phenyl)-ureido]-benzoic acid;
2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-nicotinic acid;
5-Bromo-2-(3-cyclohexyl-ureido)-benzoic acid;
2-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]-cyclohexanecarboxylic acid;
2-[3-(3-Chloro-phenyl)-ureido]-cyclohexanecarboxylic acid;
35 2-[3-(3-Bromo-phenyl)-ureido]-cyclohexanecarboxylic acid;
2-[3-(2,6-Dichloro-phenyl)-ureido]-cyclohexanecarboxylic acid;

- 2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-cyclohexanecarboxylic acid;
4-Chloro-2-[3-(thiazol-2-yl)-ureido]-benzoic acid methyl ester;
5-Bromo-2-[3-(pyridin-2-yl)-ureido]-benzoic acid methyl ester;
4-Chloro-2-[3-(5-chloro-pyridin-2-yl)-ureido]benzoic acid;
5 5-Bromo-2-(3-thiazol-2-yl-ureido)-benzoic acid methyl ester;
2-[3-(5-Bromo-pyridin-3-yl)-ureido]-4-chloro-benzoic acid;
5-Bromo-2-[3-(pyridin-2-yl)-ureido]-benzoic acid;
3-Bromo-2-[3-(2H-1 λ ⁴-thiazol-2-yl)-ureido]-benzoic acid;
3-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]-biphenyl-4-carboxylic acid amide;
10 4-[3-(3,5-Dichloro-phenyl)-ureido]-biphenyl-3-carboxylic acid;
4-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-biphenyl-3-carboxylic acid;
4-[3-(3,5-Difluoro-phenyl)-ureido]-biphenyl-3-carboxylic acid;
4-[3-(2-Chloro-phenyl)-ureido]-biphenyl-3-carboxylic acid;
4-Chloro-2-[3-(5-phenyl-2H-pyrazol-3-yl)-ureido]-benzoic acid;
15 2-[3-(2-chloro-pyridin-3-yl)-ureido]-nicotinic acid;
4-Chloro-2-[3-(2-chloro-pyridin-3-yl)-ureido]-benzoic acid;
2-[3-(4-Chloro-phenyl)-ureido]-5-iodo-benzoic acid;
5-Chloro-2-[3-(5-oxo-1-phenyl-pyrrolidin-3-yl)-ureido]-benzoic acid;
5-Bromo-2-(3-phenyl-ureido)-benzoic acid;
20 5-Bromo-2-[3-(2-fluoro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(2-chloro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3,5-dimethyl-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3,5-difluoro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3,5-dimethoxy-phenyl)-ureido]-benzoic acid;
25 5-Bromo-2-[3-(2,6-dichloro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(2-bromo-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(4-chloro-3-nitro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(4-butoxide-phenyl)-ureido]-benzoic acid;
5-Chloro-2-[3-(2-chloro-phenyl)-ureido]-benzoic acid;
30 5-Chloro-2-[3-(3,5-dimethyl-phenyl)-ureido]-benzoic acid;
2-[3-(4-Biphenyl)-ureido]-5-bromo-benzoic acid;
5-Chloro-2-[3-(3-iodo-phenyl)-ureido]-benzoic acid;
5-Chloro-2-(3-phenyl-ureido)-benzoic acid;
5-Chloro-2-[3-(2-fluoro-phenyl)-ureido]-benzoic acid;
35 5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-nicotinic acid;
5-Bromo-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]-nicotinic acid;
5-Chloro-2-[3-(3,5-difluoro-phenyl)-ureido]-benzoic acid;
5-Chloro-2-[3-(3,5-dimethoxy-phenyl)-ureido]-benzoic acid;
5-Chloro-2-[3,4-dichloro-phenyl)-ureido]-benzoic acid;

- 2-[3-(4-Butoxy-phenyl)-ureido]-5-chloro- benzoic acid;
 5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]-nicotinic acid;
 3,5-Bis-[3-(3,5-difluoro-phenyl)-ureido]- benzoic acid;
 5-Bromo-2-[3-(3,5-difluoro-phenyl)-ureido]-nicotinic acid;
 5 5-Bromo-2-[3-(2,4,6-trichloro-phenyl)-ureido]-nicotinic acid;
 5-Chloro-2-[3-(2,6-dichloro-phenyl)-ureido]-benzoic acid;
 3,5-Bis-[3-(3,5-bis-trifluoromethylphenyl)-ureido]- benzoic acid;
 2,5-Dichloro-3-[3-(3-bromo-phenyl)-ureido]-benzoic acid;
 2,5-Dichloro-3-[3-(3,5-dichloro-phenyl)-ureido]-benzoic acid;
 10 3,5-Bis-[3-(3-bromo-phenyl)-ureido]- benzoic acid
 3,5-Bis-[3-(3,5-dichloro-phenyl)-ureido]- benzoic acid;
 3-[3-(3-Bromo-phenyl)-ureido]-5-trifluoro-benzoic acid;
 3-[3-(3,5-Dichloro-phenyl)-ureido]-5-trifluoro-benzoic acid;
 3,5-Bis-[3-(3,5-bis-trifluoromethylphenyl)-ureido]- benzoic acid;
 15 2-[3-(Pyridin-3-yl)-ureido]-phenyl-boronic acid;
 2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-phenyl-boronic acid;
 2-[3-(3-Bromo-phenyl)-ureido]-phenyl-dihydroxy-borane;
 {2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
 {2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid;
 20 {2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
 {2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid
 {2-[3-(3-chloro-phenyl)-ureido]-phenyl}-phosphonic acid diethyl ester;
 {2-[3-(3-chloro-phenyl)-ureido]phenyl}-phosphonic acid;
 {2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
 25 {2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid;
 {2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
 {2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid;
 {5-Bromo-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl
 ester;
 30 {5-Bromo-2-[3-(3,5 bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid;
 {5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid
 diethyl ester;
 {5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid;
 {5-Bromo-2-[3-(3-chloro-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
 35 {5-Bromo-2-[3-(3-chloro-phenyl)-ureido]phenyl}-phosphonic acid;
 {5-Bromo-2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
 {5-Bromo-2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid;
 {5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
 {5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid;

- {5-Bromo-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]phenyl}-phosphonic acid diethyl ester;
 {5-Bromo-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]phenyl}-phosphonic acid;
 2-[[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl]-phosphonic acid dimethyl ester;
- 5 2-[[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl]-phosphonic acid;
 2-[[3-(3,5-dichloro-phenyl)-ureido]-benzyl]-phosphonic acid dimethyl ester;
 2-[[3-(3,5-Dichloro-phenyl)-ureido]-benzyl]-phosphonic acid;
 2-[[3-(3-Phenyl-ureido)-benzyl]-phosphonic acid dimethyl ester;
 2-[[3-(3-Phenyl-ureido)-benzyl]-phosphonic acid;
- 10 2-[3-(4-Chloro-phenyl)-ureido]-benzyl]-phosphonic acid dimethyl ester;
 2-[3-(4-Chloro-phenyl)-ureido]-benzyl]-phosphonic acid;
 2-[[3-(3,4-Dichloro-phenyl)-ureido]-benzyl]-phosphonic acid dimethyl ester;
 2-[[3-(3,4-Dichloro-phenyl)-ureido]-benzyl]-phosphonic acid;
 {5-Chloro-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl}-phosphonic acid
- 15 dimethyl ester;
 {5-Chloro-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl}-phosphonic acid;
 {5-Chloro-2-[3-(3,5-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
 {5-Chloro-2-[3-(3,5-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid;
 {5-Chloro-2-(3-phenyl-ureido)-benzyl]-phosphonic acid dimethyl ester;
- 20 {5-Chloro-2-(3-phenyl-ureido)-benzyl]-phosphonic acid;
 {5-Chloro-2-[3-(3,4-dichloro-phenyl)-ureido]-benzyl]-phosphonic acid dimethyl ester;
 {5-Chloro-2-[3-(4-chloro-phenyl)-ureido]-benzyl]-phosphonic acid;
 {5-Chloro-2-[3-(3,4-dichloro-phenyl)-ureido]-benzyl]-phosphonic acid dimethyl ester;
 {5-Chloro-2-[3-(3,4-dichloro-phenyl)-ureido]-benzyl]-phosphonic acid;
- 25 {2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-phenyl}-phosphonic acid diethyl ester;
 {2-[3-(2-Trifluoromethyl-phenyl)-ureido]-phenyl}-phosphonic acid diethyl ester;
 {2-[3-(2-Trifluoromethyl-phenyl)-ureido]-phenyl}-phosphonic acid;
 3-[3-(3,5-Dichloro-phenyl)-ureido]-biphenyl-4-carboxylic acid amide;
 3-[3-(2,3-Dichloro-phenyl)-ureido]-biphenyl-4-carboxylic acid amide;
- 30 3-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-biphenyl-4-carboxylic acid amide;
 {2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-phenyl}-phosphonic acid;
 [3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid;
 [3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-(5-trifluoromethyl-phenyl)-acetic acid;
 [3-(4-Chloro-3-fluoro-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid;
- 35 [3-(3,5-Dichloro-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid;
 [3-(3-Chloro-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid;
 1-(3,5-Bis-trifluoromethyl-phenylcarbamoyl)-pyrroline-2-carboxylic acid;
 1-(3,5-Bis-trifluoromethyl-phenylcarbamoyl)-4-hydroxy-pyrroline-2-carboxylic acid;
 1-(4-Chloro-3-trifluoromethyl-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid;

- 1-(3-Chloro-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid;
- 1-(3-Bromo-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid;
- 1-(3,5-Dichloro-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid;
- 1-(Cyclohexyl-carbamoyl)-pyrrolidine-2-carboxylic acid;
- 5 1-(2,6-Dichloro-pyridin-4-ylcarbamoyl)-pyrrolidine-2-carboxylic acid;
- 1-(4-Chloro-3-trifluoromethyl-phenylcarbamoyl)-4-hydroxy-pyrrolidine-2-carboxylic acid;
- 1-(3-Chloro-phenylcarbamoyl)-4-hydroxy-pyrrolidine-2-carboxylic acid;
- 1-(3-Bromo-phenylcarbamoyl)-4-hydroxy-pyrrolidine-2-carboxylic acid;
- 1-(Pyridin-3-ylcarbamoyl)-pyrrolidine-2-carboxylic acid;
- 10 N-Cyclohexyl-N'-(2,3-difluoro-4-trifluoromethyl-phenyl) urea;
- N-Cyclohexyl-N'-(2,3-difluoro-phenyl) urea;
- N-(2,3-Difluoro-4-trifluoromethyl-phenyl)-N'-(pyridin-3-yl) urea;
- N-(Pyridin-3-yl)-N'-(2,3-difluoro-phenyl) urea;
- N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-(2,3-difluoro-4-trifluoromethyl-phenyl) urea;
- 15 N-(2,6-Dichloro-pyridin-4-yl)-N'-(2,3-difluoro-4-trifluoromethyl-phenyl) urea;
- N-(2,3-Difluoro-4-trifluoromethyl-phenyl)-N'-(pyridin-4-yl) urea;
- N-(2,3-Difluoro-phenyl)-N'-(pyridin-4-yl) urea;
- N-(Cyclohexyl)-N'-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
- N-(2,6-Dichloro-pyridin-4-yl)-N'-[3-chloro-6-(1H-tetrazol-5-yl)-phenyl] urea;
- 20 N-Cyclohexyl-N'-[4'-(N'',N''-dimethyl-1-carbonyl)-2-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
- N-(2,6-Dichloro-pyridin-4-yl)-N'-[4'-(N'',N''-dimethyl-1-carbonyl)-2-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
- N-Cyclohexyl-N'-[4-bromo-2-(1H-tetrazol-5-yl)-phenyl] urea;
- 25 N-(2,6-Dichloro-pyridin-4-yl)-N'-[4-bromo-2-(1H-tetrazol-5-yl)-phenyl] urea;
- N-[5-Chloro-2-(1H-tetrazol-5-yl)-phenyl]-N'-(pyridin-3-yl) urea;
- N-[4-Bromo-2-(1H-tetrazol-5-yl)-phenyl]-N'-(pyridin-3-yl) urea;
- N-(Naphthalen-1-yl)-N'-[4'-(N'',N''-dimethyl-1-carbonyl)-3-(1H-tetrazol-5-yl)-biphenyl-4-yl] urea;
- 30 N-[2,4-Dibromo-6-(1H-tetrazol-5-yl)-phenyl]-N'-(2,6-dichloro-pyridin-4-yl) urea;
- or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any of claims 1-11, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

13. The use of a compound according to any one of claims 1-11, or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical

composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to the blockade of chloride channels.

5 14. The use according to claim 13, wherein the disease, disorder or condition responsive to the blockade of chloride channels is a disease, disorder or condition responsive to the mast cell or basophil activity, or to inhibition of angiogenesis.

15. The use according to claim 13, wherein the disease, disorder or condition
10 responsive to the blockade of chloride channels is allergic bronchopulmonary aspergillosis (ABPA), allergic rhinitis, allergic skin disease, allergic skin reaction, drug induced allergic skin reaction, anaphylaxis, asthma, atherosclerosis, atopic dermatitis (AD), bronchial asthma, cancer, chronic obstructive pulmonary disease (COPD), Chrohn's disease, contact dermatitis, dilated cardiomyopathy, fatal asthma, graft
15 rejection, hypersensitivity pneumonitis, ischemic hearth disease, pulmonary fibrosis, rheumatoid arthritis, systemic sclerosis, urticaria, uveoretinitis, cancer, metastatic cancer, prostate cancer, lung cancer, breast cancer, bladder cancer, renal cancer, colon cancer, gastric cancer, pancreatic cancer, ovarian cancer, melanoma, hepatoma, sarcoma, lymphoma, exudative macular degeneration, age-related mucular
20 degeneration, retinopathy, proliferative diabetic retinopathy, ischemic retinopathy (e.g. retinal vain or artery occlusion), retinopathy of prematurity, neovascular glaucoma, corneal neovascularization, rheumatoid arthritis, psoriasis, sickle cell anaemia, brain oedema following ischaemia or tumors, diarrhea, hypertension, diuretic hypertension, glaucoma, or ulcers.

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16. A method for the treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to responsive to the blockade of chloride channels, which method comprises the step of administering to such a living animal body in need
30 thereof a therapeutically effective amount of a compound according to any one of the claims 1-11, or any of its enantiomers or any mixture of its enantiomers, or a pharmaceutically acceptable salt thereof.